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Review Article

Benzo[1,5]thiazepine: Synthesis, Reactions, Spectroscopy, and Applications

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This review article deals with synthesis and reactions of benzo[1,5]thiazepines and the related derivatives and their applications, biological activity as well as spectroscopic data. Most of the reported data on the methods of synthesis, chemical reactions, and biological activity of these heterocycles published over the last ten years are reviewed in this paper.

1. Introduction

1,5-Benzothiazepines are the most well-known representatives of benzologs of 1,4-thiazepine and one of the three possible benzo-condensed derivatives, namely, 1,4-, 4,1- and 1,5-benzothiazepines. The parent 1,5-benzothiazepine, itself, has not hitherto been described in the literature for its pharmacological properties. However, its 2,4-disubstituted derivatives and many hydrated derivatives have been synthesized. The 1,5-benzothiazepine derivatives are of particular interest for lead discovery because they have been found active against different families of targets. The first molecule of 1,5-benzothiazepine used clinically was diltiazem, followed by clentiazem, for their cardiovascular action. Some of the 1,5-benzothiazepine derivatives were also used clinically for CNS disorders which includes thiazesim and quetiapine fumarate. Moreover, 1,5-benzothiazepine moiety is a privileged class of pharmacophore, as compounds bearing this structural unit possess a broad spectrum of biological activities such as anticonvulsant, Ca^{+2} channel antagonist, antianginal, anti HIV, squalene synthetase inhibitor, V_2 arginine vasopressin receptor antagonist, and HIV-1 reverse transcriptase inhibitor [1–3].

The methods for the preparation of 1,5-benzothiazepines can be divided into two major groups, namely, the construction of a seven-membered heteroring from the elements of open chains, and reactions involving ring expansion.

2. Nomenclature and Way of Numbering

1,5-Benzothiazepines are the most well-known representatives of benzologs of 1,4-thiazepine. According to the IUPAC nomenclature, the benzo[1, 5]thiazepine structures **IA** or **IB** may be named as (*Z*)-2,3-dihydrobenzo[*b*][1, 4]thiazepine or (*Z*)-2,3-dihydro-substituted-benzo[*b*][1, 4]thiazepine. Also, the substituted-benzo[1, 5]thiazepines structure **IIA** or **IIB** may have the name: 2,3,4,5-tetrahydrobenzo[*b*][1, 4]thiazepine or 2,3,4,5-tetrahydro-substituted-benzo[*b*][1, 4]thiazepine (see Figure 1).

3. Preparation of 1,5-Benzothiazepine System and Its Related Derivatives

3.1. Thiophenol and Its Derivative Approaches

3.1.1. Solid Phase Synthesis: Claisen-Schmidt Condensation of 3-Hydroxyacetophenone with Different Substituted Aldehydes and o-Aminothiophenol. The solution phase synthesis of 2,3-dihydro-1,5-benzothiazepines **4** and **5** was carried out by heating under reflux of α,β-unsaturated ketones **3** (obtained from reaction of an aldehyde and the acetophenones **2**) with *o*-aminothiophenol in dry acidic MeOH in the presence of drops of glacial CH_3COOH. Also, the synthesis of 2,3-dihydro-1,5-benzothiazepines **9** was carried out on Wang

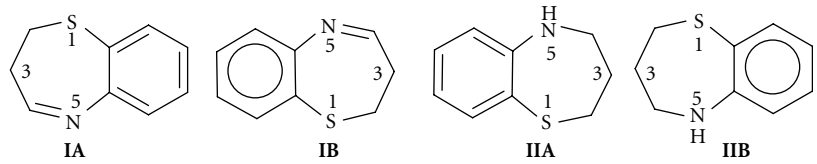
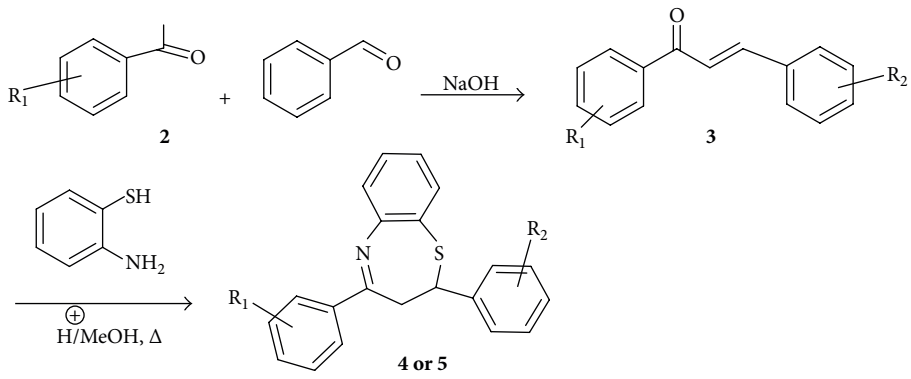
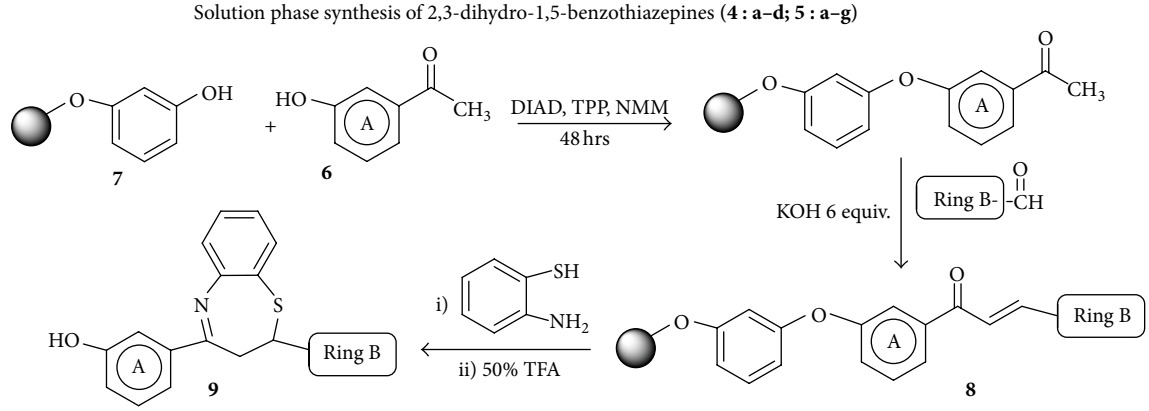


Figure 1



Solution phase synthesis of 2,3-dihydro-1,5-benzothiazepines (**4 : a–d; 5 : a–g**)



Solid phase synthesis of 3′-hydroxy-2,3-dihydro-1,5-benzothiazepines **9**(**a–p**)

4	R_1	R_2
(a)	H	H
(b)	H	4-Me
(c)	H	3,4-diOMe
(d)	H	4-NO_2

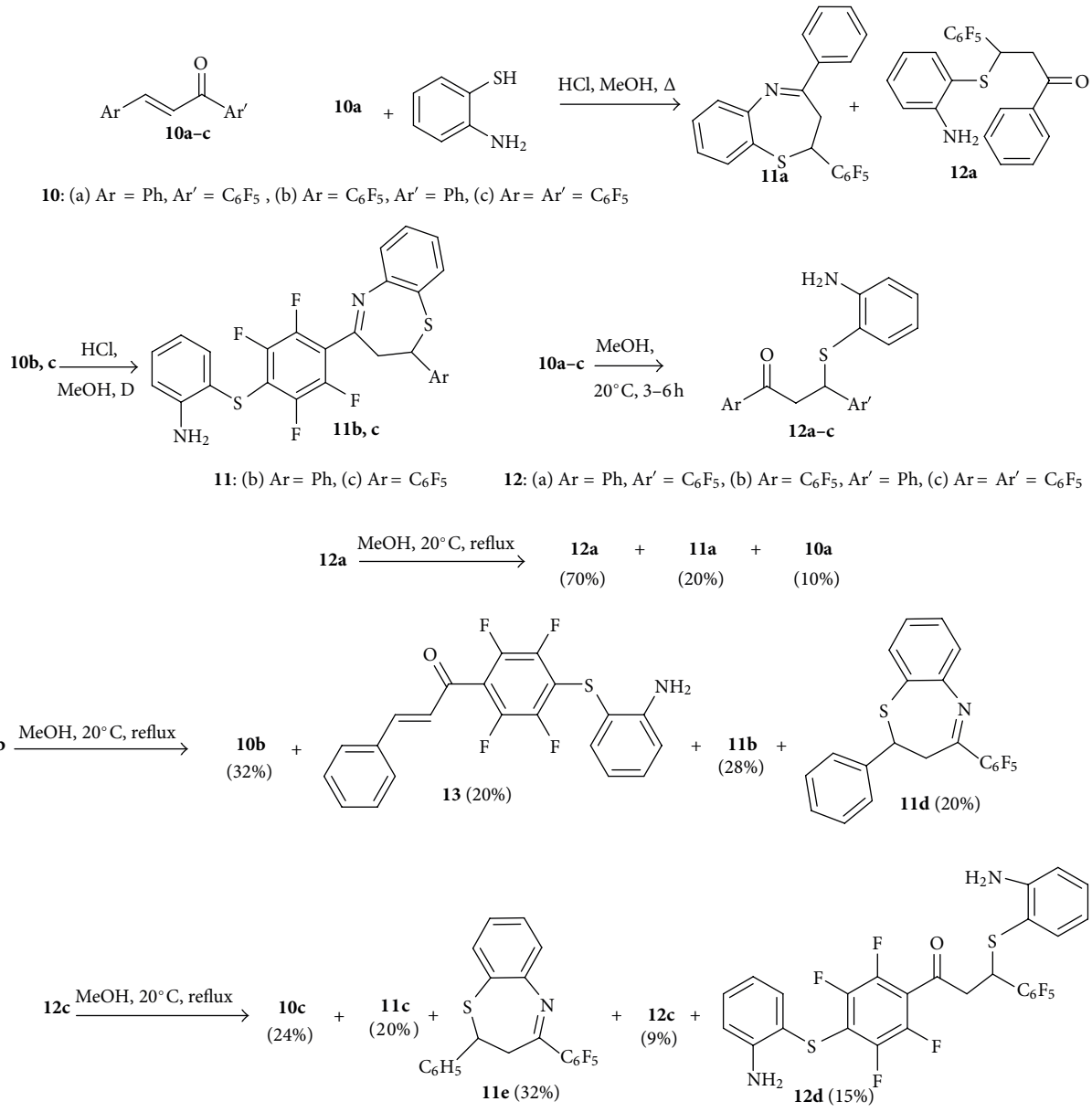
5	R_1	R_2
(a)	2-OH	H
(b)	2-OH	4-Cl
(c)	2-OH	4-F
(d)	2-OH	3-OMe
(e)	2-OH	4-OMe
(f)	2-OH	4-Me
(g)	2-OH	3,4-OCH_2O

1,5-Benzothiazepines **9**	
Ring B	Ring B
(a) = Phenyl	**(i)** = 3,4-$OMe_2C_6H_4$
(b) = 2-ClC_6H_4	**(j)** = 4-OH-3-$OMeC_6H_4$
(c) = 3-ClC_6H_4	**(k)** = 3-$NO_2C_6H_4$
(d) = 4-ClC_6H_4	**(l)** = 4-$NO_2C_6H_4$
(e) = 2-FC_6H_4	**(m)** = 4-MeC_6H_4
(f) = 3-OHC_6H_4	**(n)** = 4-$NMe_2C_6H_4$
(g) = 4-OHC_6H_4	**(o)** = Pyridin-3-yl
(h) = 2-$OHCH_3C_6H_4$	**(p)** = Thien-2-yl

Scheme 1: Solid phase synthesis: Claisen-Schmidt condensation of 3-hydroxyaceto-phenone with different substituted aldehydes and *o*-aminothiopheno.

resin using chalcones **8** as precursors which in turn were synthesized on the same solid support through Claisen-Schmidt condensation of 3-hydroxyacetophenone **6** with different substituted aldehydes **7** [4] (Scheme 1).

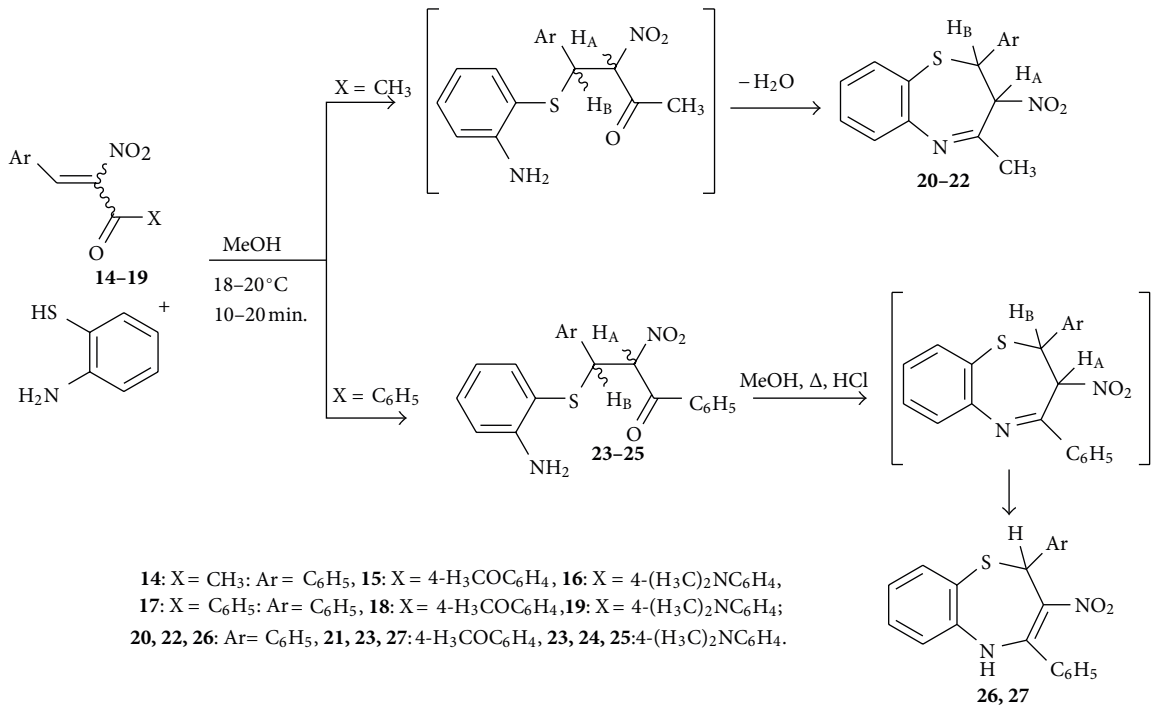
3.1.2. Reactions of Polyfluorinated Chalcones with o-Aminobenzenethiol and Its Zinc Salt. Chalcone **10a** on heating under reflux with 2 moles of *o*-aminothiophenol produced equal amounts of the benzo[*b*][1, 5]thiazepine **11a**



Scheme 2: Reactions of polyfluorinated chalcones with *o*-aminobenzenethiol and its zinc salt.

(5% yield) and 3-(2-aminophenylthio)-3-(perfluorophenyl)-1-phenylpropan-1-ol **12a**. Reaction of **10b** with *o*-aminothiophenol (2-moles) afforded 1,5-benzothiazepine **11b** in 88% yield. When a threefold excess of the reactant was used in the reaction of **10c** with *o*-aminothiophenol the benzo[*b*][1, 5]thiazepine **11c** was afforded (80% yield). To reveal the sequence step of formation of benzothiazepines, the thia-adducts **12a–c** were synthesized by the reaction of chalcones **10a–c** with *o*-aminothiophenol in MeOH at 20°C for 3–6 h. The thia-adduct **12a** under reflux in MeOH in presence of HCl underwent partial ring closure to form benzothiazepine **11a** and partially **12a** transformed into chalcone **10a**; however, the most part of **12a** remains unchanged. The adduct **12b** under the same reaction conditions was completely consumed and the reaction mixture contained chalcone **10b**, 1-(4-(2-aminophenylthio)-2,3,5,6-tetrafluorophenyl)-3-phenylprop-2-en-1-one **13** together with thebenzo[1, 5]thiazepines **11b,d**. Also, the same reaction of the adduct **12c** under reflux formed a complicated mixture of products containing chalcone **10c**, thia-adducts **12c,d**, and benzothiazepines **11c,e** [5] (Scheme 2).

3.1.3. Reaction of Gem-Acetyl- and Gem-Benzoylnitrostyrenes with o-Aminothiophenol. The chemical behavior of nitrogen ketones was investigated *via* reactions of *gem*-acetyl- and *gem*-benzoylnitro styrenes **14–19** with *o*-aminothiophenol. These reactions proceed successfully at equimolar ratio of reagents under very mild conditions at 18–20°C in methanol, in the absence of a catalyst, in 10–20 min, to



Scheme 3: Reaction of *gem*-acetyl- and *gem*-benzoylnitrostyrenes with *o*-aminothiophenol.

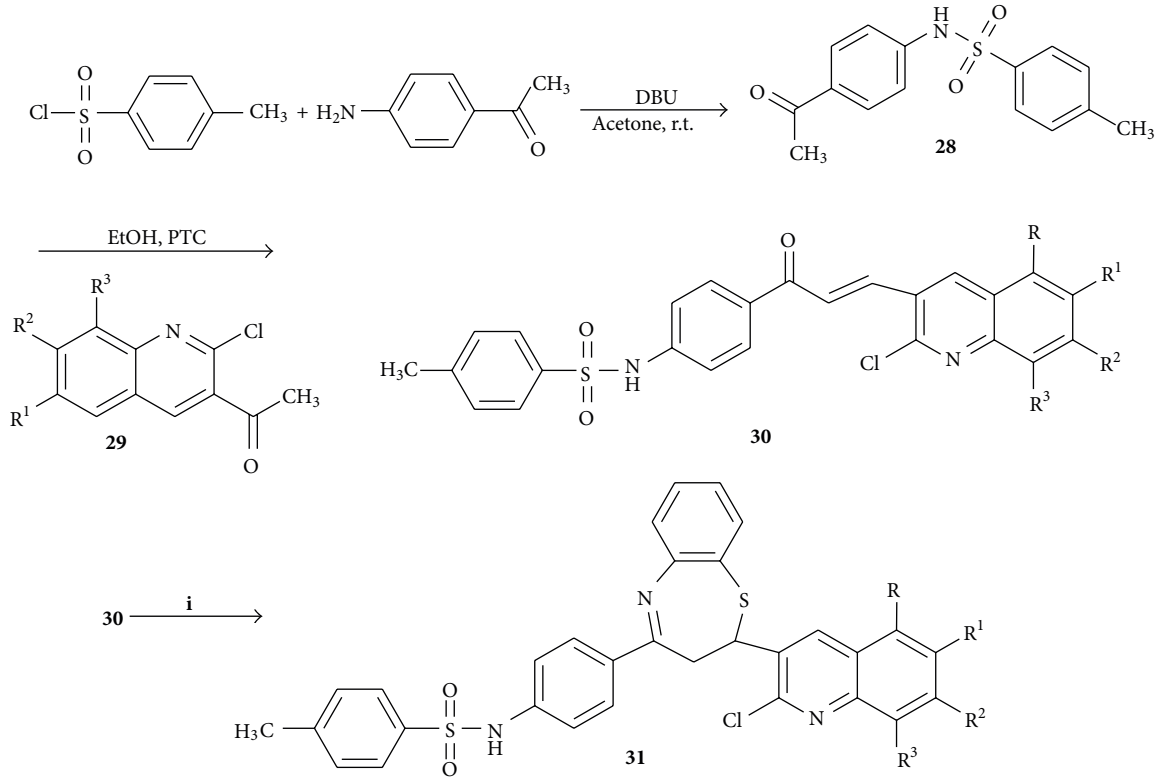
form new compounds **20–24**, respectively. However, while the *gem*-acetylnitro-styrenes **14–16** afford 2-aryl-4-methyl-3-nitro-2,3-dihydro-1,5-benzothiazepines **20–22**, from the *gem*-benzoylnitrostyrenes **17–19** linear *S*-adducts **23–25** were obtained in 80–98% yield. Apparently, the reaction of *o*-aminothiophenol with *gem*-acylnitro-styrenes **14–19** lead initially to the formation of an adduct at the multiple C=C bond (Ad_N), which was isolated in the case of compounds with the benzoyl group **23–25**, and the adducts obtained from the *gem*-acetylnitrostyrene **14–16** immediately suffers heterocyclization. This may be due to the difference in activity of carbonyl groups in the benzoyl and acetyl functions of the addition products. Probably, the attack of amino group on the benzoyl carbonyl group in the adducts **23–25** is difficult compared to the acetyl analogs due to steric and electronic factors.

In order to obtain nitrobenzothiazepine structures with phenyl substituent at the C4 atom, the linear *S*-adducts **23** and **24** when heated under reflux in EtOH in the presence of methanolic HCl for 1–3 h 2-aryl-3-nitro-4-phenyl-2,5-dihydro-1,5-benzothia-zepines **26** and **27**, were obtained, respectively [6] (Scheme 3).

3.1.4. Cyclocondensation Reaction of (E)-N-(4-(3-(2-Chloro-5, 6,7,8-substituted-quinolin-3-yl)acryloyl)phenyl)-methylbenzenesulfonamide with 2-Aminothiophenol in Ethanol in Presence of Bi-Catalyst. The 2-chloro-substituted-quinoline chalcones **30** were prepared from condensation of 4-methyl sulphonamido acetophenone **28** and quinonline-3-carbaldehyde **29** in alcoholic KOH. Cyclo-condensation of the chalcones **30** with *o*-aminothiophenol in the presence of a bicatalyst afforded the benzothiazepines **31** in good yield [7] (Scheme 4).

3.1.5. Cyclocondensation of 1-(4-(Methylsulfonyl)phenyl)-2-tosyl-3-(3,4,5-trisubstituted phenyl)prop-2-en-1-ones with 2-Aminothiophenol in Refluxing Toluene Using Catalytic Amounts of Trifluoroacetic Acid. Condensation of 2-bromo-1-(4-(methylsulfonyl)phenyl)ethanone **32** and 4-methyl sodium benzene sulfinate **33** gave 1-(4-(methylsulfonyl)phenyl)-2-tosylethanone **34**. Claisen-Schmidt condensation of **34** with aryl aldehydes in the presence of piperidine in CH_2Cl_2 gave the intermediates 1-(4-(methylsulfonyl) phenyl)-2-tosyl-3-(3,4,5-trisubstituted-phenyl)prop-2-en-1-ones **35a–f** in excellent yields. Cyclo-condensation of **35a–f** and *o*-aminothiophenol in refluxing toluene using CF_3COOH catalyst gave better yields of 2-(substituted phenyl)-3-[(methyl phenyl) sulfonyl][(methyl sulfonyl) phenyl]-2,3-dihydro-1,5-benzothiazepines **36a–f** (Method A). Also, the neat cyclo-condensations of the chalcones **35** supported on silica-gel with *o*-aminothiophenol occurred rapidly at 80°C and gave better yields of the desired tri-substituted 1,5-benzothiazepines **36a–f** (Method B) [8] (Scheme 5).

3.1.6. Cyclo-Condensation Reaction of the Phenolic β-Diketones with o-Aminothiophenol. Cyclo-condensation of the Phenolic *β*-diketones **37a–d** with *o*-aminothiophenol proceeded under oxidation to give oxygen-bridged 1,5-benzothiazepines **39a–d** in a reasonable yield, whereas the respective compounds **38a–d** and **40a–d** were not detected [9] (Scheme 6).



(i) *o*-Aminothiophenol **1**, piperidine, AcOH, EtOH, reflux

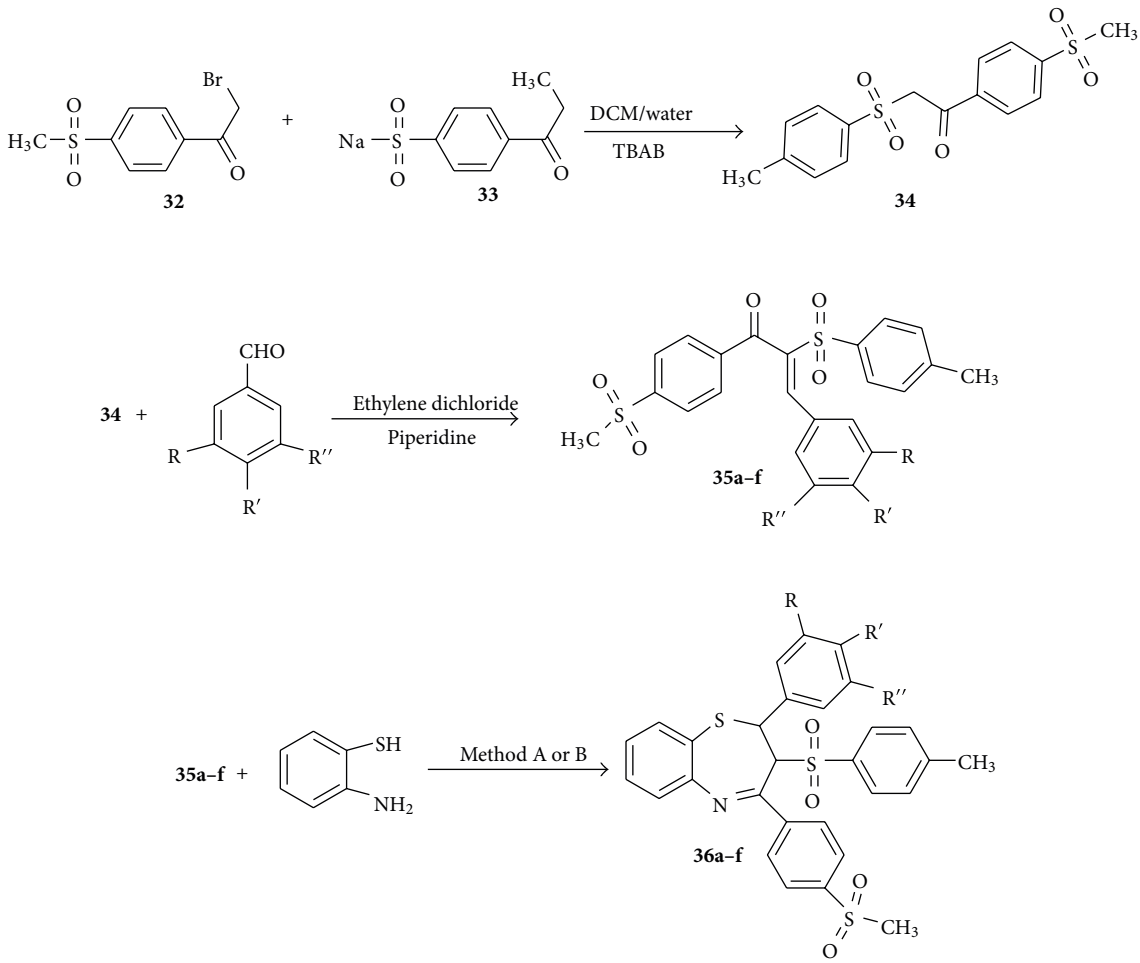
31	R	R^1	R^2	R^3	Yield (%)
(a)	H	H	H	H	75
(b)	H	H	CH_3	H	66
(c)	H	OCH_2CH_3	H	H	68
(d)	H	Cl	H	H	62
(e)	H	H	H	CH_3	70

Scheme 4: Cyclocondensation reaction of (*E*)-*N*-(4-(3-(2-chloro-5,6,7,8-substituted-quinolin-3-yl)acryloyl)phenyl)-methylbenzenesulfonamide with 2-aminothiophenol in ethanol in presence of bi-catalyst.

3.1.7. Thermal Reaction of (Z)-1,3-Diphenyl-2-(1H-1,2,4-triazol-1-yl)prop-2-en-1-one with o-Aminothiophenol in the Presence of CF_3COOH. 1-Phenyl-2-(2*H*-1,2,3-triazol-2-yl) ethanone **41** when heated under reflux with benzaldehyde and catalytic amount of piperidine gave 1,3-diphenyl-2-(1*H*-1,2,4-triazol-1-yl)prop-2-en-1-one **42**. The latter triazole upon thermal reaction with *o*-aminothiophenol and CF_3COOH for 5-6 h yielded 1,5-benzothiazepine containing 1,2,4-triazole moiety **43** (**43′** toutemeric form in solvent) in 72.7% yield [10] (Scheme 7).

3.1.8. Reaction of 1-(2-Phenyl-2H-1,2,3-triazol-4-yl)-3-(p-substituted-phenyl)prop-2-en-1-ones with o-Aminothiophenol, in EtOH under Reflux in the Presence of CF_3COOH. 1-(2-Phenyl-2*H*-1,2,3-triazol-4-yl)-3-(*p*-substituted-phenyl)prop-2-en-1-ones **44a–d** (prepared from the desired aromatic aldehydes and 1-(2-phenyl-2*H*-1,2,3-triazol-4-yl)ethanone) on reaction with *o*-aminothiophenol, in EtOH under reflux in the presence of CF_3COOH gave 2,3-dihydro[1, 5]benzothiazepines **45a–e** in good yield (Scheme 8) [11] (Scheme 8).

3.1.9. Thermal Reaction of (E)-1-(2-Phenyl-2H-1,2,3-triazol-4-yl)-3-(p-substituted-phenyl)prop-2-en-1-ones with o-Aminobenzenethiol in Presence of CF_3COOH. The α,β-unsaturated carbonyl compounds **48a–c** were prepared by a condensation reaction of 4-acetyl-2-phenyl-1,2,3-triazole **46** with substituted aldehydes **47a–c**. Preparation of the carbonyls **48d,e** using the same method failed and instead gave Michael type addition products **50d,e** as major compounds. Successful preparation of **48d** and **e** was fulfilled *via* dropping of 4-acetyl-2-phenyl-1,2,3-triazole **46** into solutions of the aldehydes **47d,e** in EtOH slowly. The triazoles **48a–e** upon heating with *o*-aminothiophenol in presence of CF_3COOH in ethanol (5-6 h) afforded the



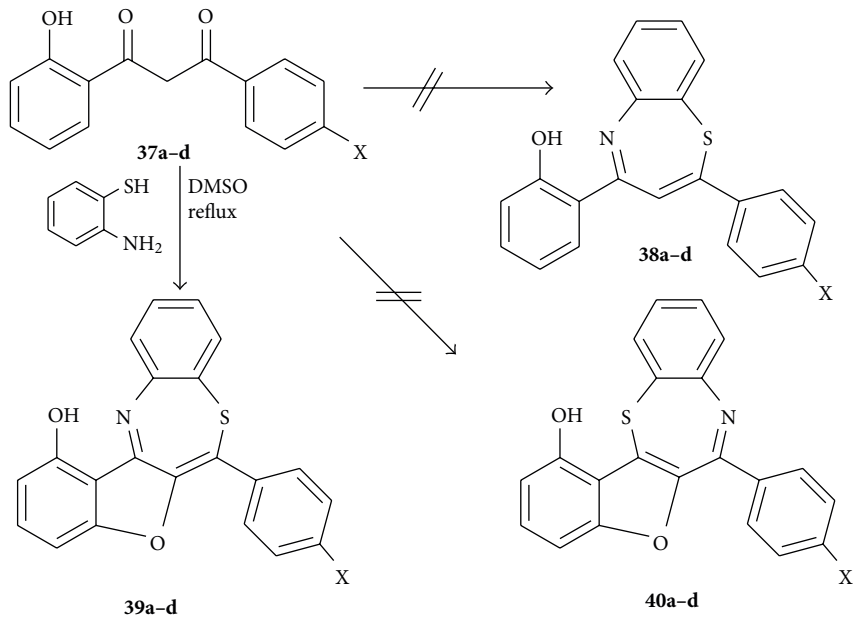
Characterization data of 1-[(4′-methylsulfonyl)phenyl]-2-[(4-methylphenyl)-sulfonyl]-prop-2-en-1-ones **35a–f**.

35	R	R′	R′′	Yield (%)	HPLC Purity (%)
(a)	H	F	H	55	98
(b)	OCH_3	OCH_3	OCH_3	52	92
(c)	H	OCH_3	OCH_3	53	93
(d)	H	OH	H	50	88
(e)	H	OCH_3	H	60	96
(f)	H	Cl	H	54	91

Characterization data of 2-(substitutedphenyl)-3-[(methylphenyl)sulfonyl] [(methylsulfonyl)phenyl]-2,3-dihydro-1,5-benzothiazepines **36a–f**.

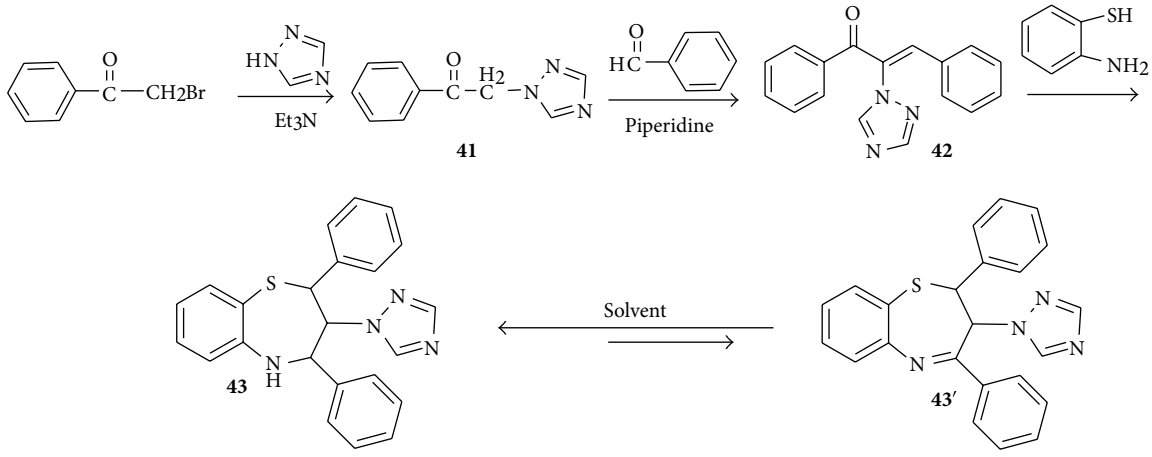
36	R	R′	R′′	Yield (%)		HPLC purity (%)
				Method A	Method B	
(a)	H	F	H	60	76	88
(b)	OCH_3	OCH_3	OCH_3	54	64	86
(c)	H	OCH_3	OCH_3	56	69	87
(d)	H	OH	H	59	72	83
(e)	H	OCH_3	H	61	78	88
(f)	H	Cl	H	51	59	84

Scheme 5: Cyclocondensation of 1-(4-(methylsulfonyl)phenyl)-2-tosyl-3-(3,4,5-trisubstituted-phenyl)prop-2-en-1-ones with *o*-aminothiophenol in refluxing toluene using catalytic amounts of trifluoroacetic acid.



X = **(a)** H, **(b)** Cl, **(c)** F, **(d)** OCH_3

Scheme 6: Cyclo-condensation reaction of the phenolic β-diketones with *o*-aminothiophenol.

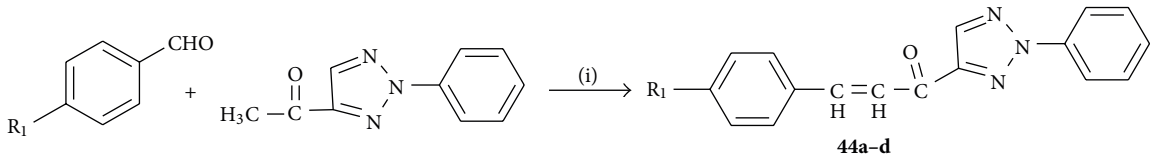


Scheme 7: Thermal reaction of (*Z*)-1,3-diphenyl-2-(1*H*-1,2,4-triazol-1-yl)prop-2-en-1-one with *o*-aminothiophenol in presence of CF_3COOH.

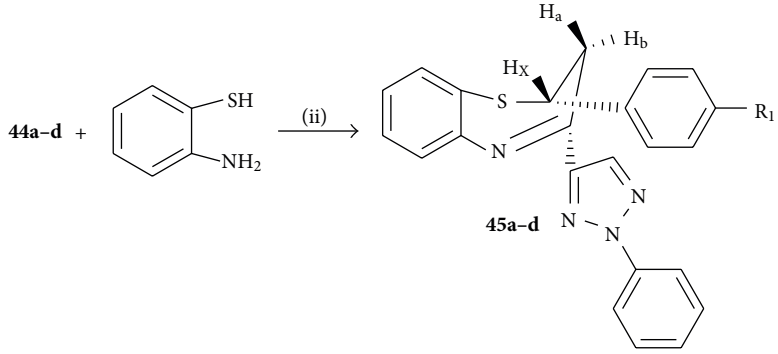
(*E*)-4-(2-phenyl-2*H*-1,2,3-triazol-4-yl)-2-(*p*-substituted-phenyl)2,3dihydrobenzo[1, 5]thiazepines **49a–e** in good yield [12] (Scheme 9).

3.1.10. Reaction of Chalcones with 2-Aminothiophenol Derivatives in the Presence of Fluoroboric Acid Adsorbed on Silica-Gel (HBF_4–SiO_2). When chalcones of type **51** were treated with *o*-aminothiophenol in the presence of fluoroboric acid adsorbed on silica-gel (HBF_4–SiO_2) selective thia-Michael addition to the α,β-unsaturated carbonyl moiety took place to form the corresponding adducts **52** in excellent yields. The latter adducts when heated under reflux in MeOH/HBF_4–SiO_2 gave the corresponding 2,3-dihydro-1,5-benzothiazepines **53** in high yields through a one-pot cycloaddition reaction [13] (Scheme 10).

3.1.11. Reaction of 3-(2-Phenoxyquinolin-3-yl)-1-p-substituted-prop-2-en-1-ones with o-Aminothiophenol in Ethanol Using Acetic Acid as Catalyst. 2-Chloro-3-quinolinecarbaldehyde



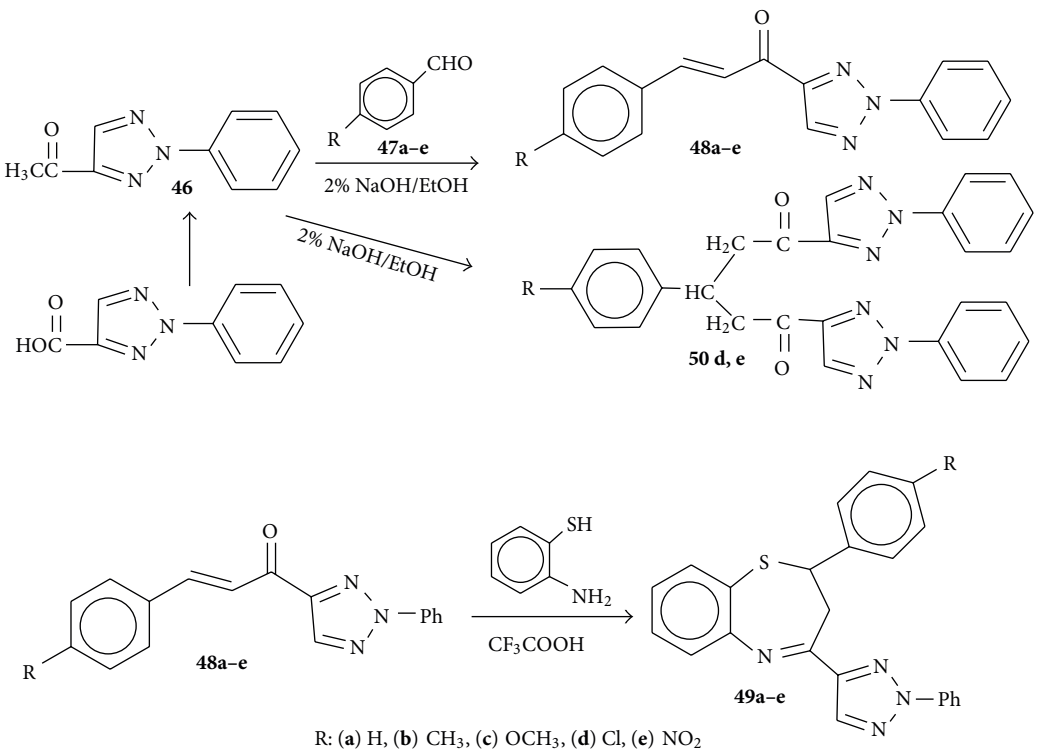
(i) (1) EtOH, NaOH (2%), stirring at r.t.(2-3 h); (2) neutralization tp pH 7



45	R_1	Yield
(a)	H	76
(b)	OMe	81
(c)	Cl	80
(d)	NO_2	79

(ii) Ethanol, stirring for 20–30 min, CF_3COOH, reflux for 5-6 h

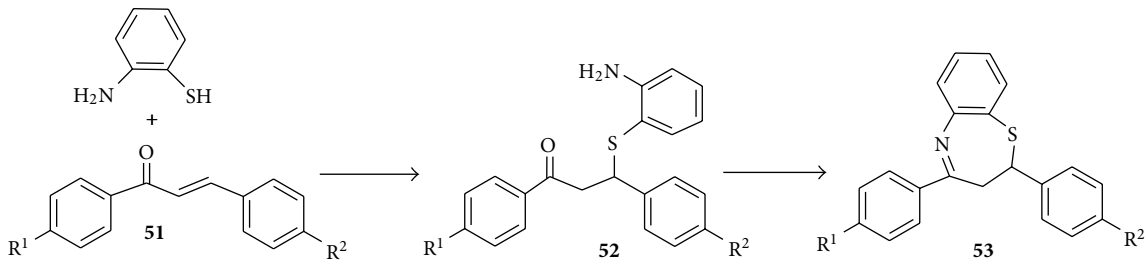
Scheme 8: Reaction of 1-(2-phenyl-2*H*-1,2,3-triazol-4-yl)-3-(*p*-substituted-phenyl)prop-2-en-1-ones with *o*-aminothiophenol, in EtOH under reflux in the presence of CF_3COOH.



R: (**a**) H, (**b**) CH_3, (**c**) OCH_3, (**d**) Cl, (**e**) NO_2

Scheme 9: Thermal reaction of (*E*)-1-(2-phenyl-2*H*-1,2,3-triazol-4-yl)-3 (*p*-substituted-phenyl)prop-2-en-1-ones with *o*-aminobenzenethiolin presence of CF_3COOH.

54 reacted with phenol in presence of an alkali to give 2-phenoxy-3-quinolinecarbaldehyde **55**. The α,β-unsaturated ketones **56a–c** were synthesized *via* Claisen-Schmidt condensation between the phenoxy derivative **55** and 1-arylethanones. Equimolar quantities of **56a–c** and *o*-aminothiophenol in ethanol using CH_3COOH as catalyst afforded satisfactory yields of the 1,5-benzothiazepine derivatives **57a–c** [14] (Scheme 11).

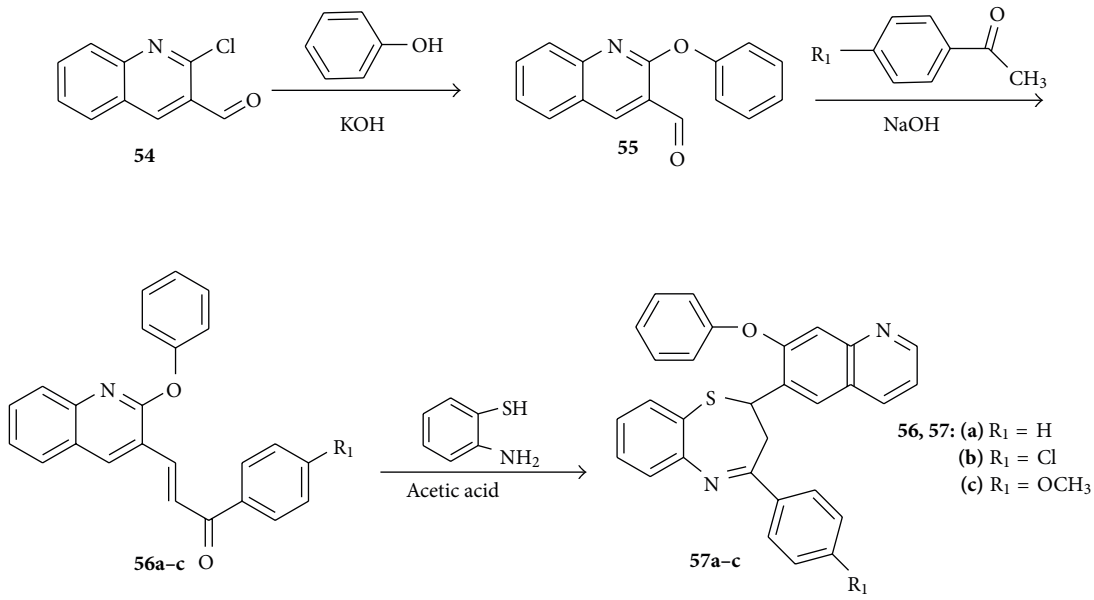


One-pot synthesis of 2,3-dihydro-1,5-benzothiazepines **53**.
HBF_4–SiO_2-catalysed one-pot synthesis of 2,3-dihydro-1,5-benzothiazepines by reaction of 1,3-diaryl-2-propenones with o-aminothiophenol

51[(a)],**52,53**	R^1	R^2	Time (h)	Yield of **53**[(b)]
(a)	H	H	4	81
(b)	H	Cl	5	89
(c)	Cl	H	4	82
(d)	H	NO_2	5	88
(e)	H	OMe	6	89
(f)	OMe	H	6	87

[(a)] 1,3-Diaryl-2-propanonein MeOH treated with *o*-aminothiophenol in thepresenceof HBF_4-SiO_2; [(b)] Isolated yield of 2,3-dihydro-1,5-thiazepines after chromatographic purification.

Scheme 10: Reaction of chalcones with *o*-aminothiophenol derivatives in the presence of Fluoroboric acid adsorbed on silica-gel (HBF_4–SiO_2).



Scheme 11: Reaction of 3-(2-phenoxyquinolin-3-yl)-1-*p*-substituted-prop-2-en-1-ones with *o*-aminothiophenol in ethanol using acetic acid as catalyst.

3.1.12. Thermal Reaction of 5-Aryl-2,4-bis(arylmethylidene) Dihydro-3-thiophenones and o-Aminothiophenol in Acetic Acid Compared to Same Reaction Performed under Solvent-Free Microwave Irradiation. The benzothiazepines **58** were synthesized in 55–91% yields upon heating under reflux 5-aryl-2,4-bis(arylmethylidene) dihydro-3-thiophenones **60** with *o*-aminothiophe-nol in a 1:1.5 molar ratio in CH_3COOH for 45–60 min.

For comparison, when the thiophenone **60** and *o*-aminothiophenol in the same molar ratio and CH_3COOH

catalyst were thoroughly mixed and irradiated while stirring in a microwave oven for 2-3 min at maximum 84°C; the benzothiazepine derivatives **58** were afforded in moderate yields (42–62%). Therefore, the reaction under microwave irradiation proceeded rapidly but led to a lower yield of the desired benzothiazepine products compared with the thermal reaction.

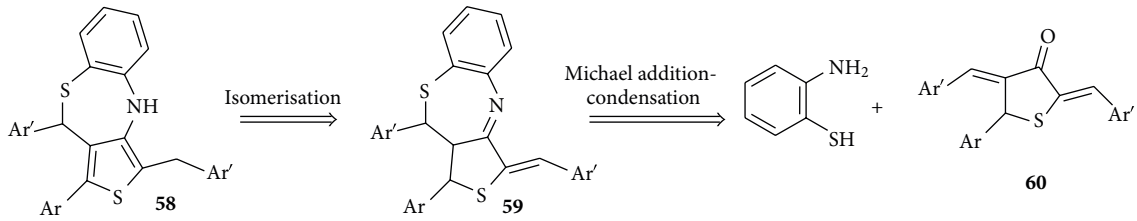
The tandem reaction leading to **58** presumably proceeds through an initial Michael addition of *o*-aminothiophenol to 5-aryl-2,4-bis(arylmethylidene)dihydro-3-thiophenones **60** affording **61** with concomitant condensation to afford **63** either directly from **62** or through **59**. Presumably, the aromatic stability of the thiophene ring provides the impetus for the isomerization of **63** to furnish **58**. It is pertinent to note that thieno-benzothiazepine **64**, a regioisomer of **58** arising from initial Michael addition of **60** to the other benzylidene C=C bond at the 2-position of **60**, was not formed, even in traces, in this reaction. This selectivity could probably be ascribed to the conjugation of the sulfur in the five-membered ring with the proximate C=C bond diminishing the electrophilicity and the reactivity of the C=C bond towards the initial Michael addition, which, in turn, determines the regioisomer formed in this tandem sequence. The aromatic stability of the thiophene ring of **58** is envisaged to trigger the isomerization of **59** in the presence of acetic acid [15] (Scheme 12).

3.1.13. Improved Synthesis of 1,5-Benzothiazepines Using Ceric Ammonium Nitrate (CAN). Reaction of chalcone **65a** with *o*-aminothiophenol at 60–65°C in the absence of ceric ammonium nitrate (CAN) catalyst did not proceed after extensive long reaction times (8–10 h) with lower yield of the desired 1,5-benzothiazepin. Meanwhile, upon using 2 mol or 6 mol% of CAN catalyst, the conversion to 1,5-benzothiazepine was 70% and 85% yield, respectively. Continuation of subsequent condition optimization revealed that 10 mol% of CAN catalyst was sufficient to complete the reaction and the best result obtained **66a** in ethanol after ultrasonic irradiation was 93% without any undesirable side product being observed. Therefore, attempts were continued to examine this reaction generality through reactions of several substituted homocyclic **65b–h** and heterocyclic **65i–k** chalcones with *o*-aminothiophenol. The obtained results were compatible with various substituents such as F, NO_2, Cl, CH_3, and OCH_3 and no competitive nucleophilic cleavage was observed for the substrate having an aryl, CH_3 or OCH_3 groups. Also, the case of electron donating substituents resulted in longer reaction times, and the electron withdrawing substituents required shorter time for the complete reaction. Moreover, no significant substituent effects were observed in case of hetero-aryl aldehydes. Generally, this method offers significant advantages over the other method including the fact that (i) the reaction is simple to execute; (ii) the 1,5-benzothiazepine products are isolated in good to excellent yields; (iii) the work-up is simple; (iv) the reaction time is short (32–38 min); (v) the 1,5-benzothiazepines are obtained in excellent purity [16] (Scheme 13).

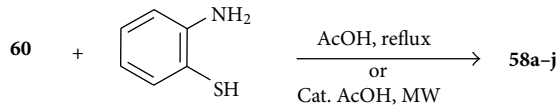
3.1.14. Reaction of 1-(2-Hydroxy-3,4,5-trisubstituted-phenyl)-3-(4-(phenylthio)phenyl)-prop-2-en-1-ones with o-Aminothiophenol in Ethanol under Ultrasonic Irradiation via a [4 + 3] Annulation. To prove that the ultrasonic irradiation plays an important role in the synthesis of 1,5-benzothiazepines a model optimum experimental conditions for the reaction of chalcones of type **69** (prepared from 4-(phenylthio)benzaldehyde **68** and *o*-hydroxy acetophenones **67**) reaction of chalcone **69a** with *o*-aminothiophenol in EtOH was tried. The results indicated that 30 min and a temperature of 65°C were sufficient to obtain high yield of the 1,5-benzothiazepine product **70a** (93%). In comparison, upon using conventional method, the yield of **70a** was 57% after heating 4-5 h at 65°C. Similarly, the thiazepines **70b–g** were synthesized in good yield from **69b–g** and *o*-aminothiophenol in EtOH under ultrasonic irradiation method. A proposed Mechanism was outlined for the synthesis of the thiazepines *via* [1, 4] and [1, 2] addition of *o*-aminothiophenol to the chalcones **69** under ultrasonic irradiation [3] (Scheme 14).

3.1.15. Thermal Reaction of 1-(2,4-Disubstituted-phenyl)-3-(p-substituted-phenyl)prop-2-en-1-ones with 2-Aminothiophenol in the Presence of a Catalytic Amount of Nanocrystalline Al_2O_3. Reaction of 1-(2,4-disubstituted-phenyl)-3-(*p*-substituted-phenyl)prop-2-en-1-ones **71a–h** with *o*-aminothiophenol (2.5 : 1 molar ratio) in the presence of a catalytic amount of nanocrystalline Al_2O_3 in water, while stirring at room temperature for the appropriate time afforded the corresponding 1,3-diaryl-2,3-dihydro-1,5-benzothiazepines **72a–h** in good to excellent yield. This reaction was found compatible with various electron-donating and electron-withdrawing substituents, and assumed to start by 1,4-Michael addition of the SH on the C=C bond followed by the condensation of the NH_2 on the carbonyl group. It is worthy to note that using nanocrystalline Al_2O_3 is preferable than commercially available bulk Al_2O_3 or basic Al_2O_3 due to its increased catalytic activity and could be reused for four cycles without loss of activity and selectivity [17] (Scheme 15).

3.1.16. MW-Assisted Condensation Reactions of o-Aminothiophenol with Carbonyl Compounds in the Presence of Erbium (III) Triflate. Condensation reactions of simple ketones (acetone, acetophenone, *p*-nitro- and *p*-methoxy acetophenones) with *o*-aminothiophenol in presence of erbium (III) triflate ($Er(OTf)_3$) catalyst while stirring at room temperature for 3 h gave no 1,5-benzothiazepine products **73** or **74a–c**. These reactions in fact lead to the corresponding Schiff bases without further cyclization to form the desired 1,5-benzoheteroazepine. In contrast, the stirred reaction of chalcone **75a** with *o*-aminothiophenol using $Er(OTf)_3$ under solvent-free microwave-assisted condensation process, (1000 W) for 30 min. at room temperature led to the cyclized 1,5-benzothiazepines **76a** as fair yield product. Whereas very good results were obtained for the more reactive substrates **75b** and **c** (highly electron rich), confirming the synthesis of



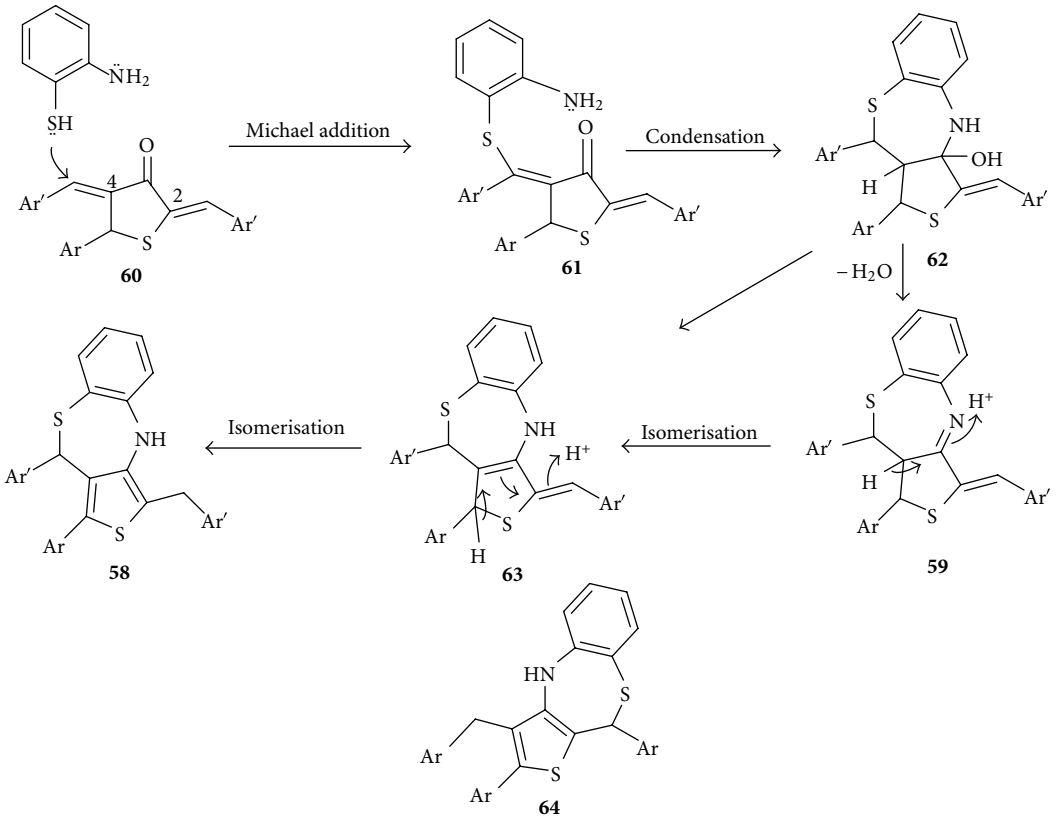
Retrosynthesis of thienobenzothiazepines **58**



3-Benzyl-1,10-diaryl-4*H*, 10*H*-thieno[3,4-*c*][1,5]benzothiazepines **58**

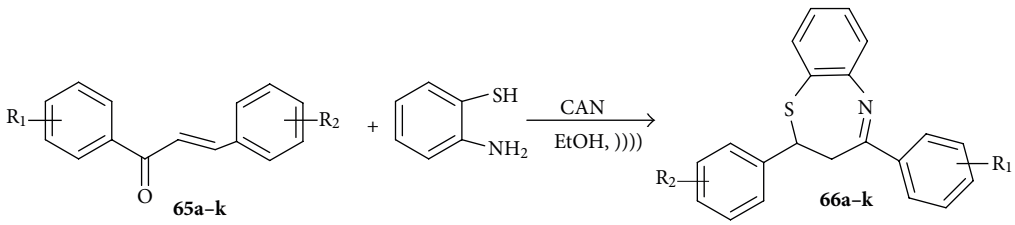
58	Ar	Ar′	Reaction time (min)		Yield[(c)] (%)	
			MW Reflux[(a)]	ACOH reflux	MW[(b)]	AcOH
(a)	C_6H_5	C_6H_5	2	50	53	65
(b)	C_6H_5	*p*-MeC_6H_4	2	50	48	55
(c)	C_6H_5	*p*-MeC_6H_4	2	45	54	88
(d)	C_6H_5	*p*-$MeOC_6H_4$	3	60	42	91
(e)	C_6H_5	*p*-FC_6H_4	2	60	54	56
(f)	C_6H_5	*o*-MeC_6H_4	3	60	47	58
(g)	C_6H_5	*o*-$MeOC_6H_4$	2	50	50	62
(h)	*p*-MeC_6H_4	*p*-MeC_6H_4	3	60	62	73
(i)	*p*-ClC_6H_4	*p*-MeC_6H_4	2	45	60	72
(j)	*o,p* -$Cl_2C_6H_3$	*p*-ClC_6H_4	2	45	59	74

[(a)] Irradiated with a catalytic amount of acetic acid; [(b)] yield after column chromatographic purification; [(c)] yield after crystallization



Mechanism for formation of thienothiazepines **58**

Scheme 12: Thermal reaction of 5-aryl-2,4-bis(arylmethylidene) dihydro-3-thiophenones and *o*-aminothiophenol in acetic acid compared to same reaction performed under solvent-free microwave irradiation.



Synthesis of 1,5-benzothiazepines **66** from chalcones and *o*-aminothiophenol.

66	R_1	R_2	Time		Yield (%)	
			With US (min)	Without US (hr)	With US (min)	Without US (hr)
(a)	H	H	32	8-9	93	71
(b)	H	*p*-F	30	6–8	89	64
(c)	*p*-NO_2	H	328	8-9	86	72
(d)	*p*-OMe	*p*-OMe	37	8–10	79	64
(e)	*p*-OMe	*p*-CH_3	34	6-7	81	62
(f)	*p*-OMe	*p*-Cl3	0	7–9	87	68
(f)	H	Thinyl	38	9-10	91	70
(h)	*p*-F	2-OH,4-CH_4' 5-Cl	28	5-6	89	71
(i)	2,4-Cl,5-OH	*p*-Pyrazolyl	341	1–3	87	75
(j)	1-OH, 4-Br	2-*p*-(Tolyloxy)-quinoline	31	2–4	85	71
(k)	2,4-Cl, 5-OH	6-Methyl-2-(1H-pyrazole-1-yl) quinoline	30	2–4	87	68

US: ultrasonic irradiation

Scheme 13: Improved synthesis of 1,5-benzothiazepines using ceric ammonium nitrate (CAN).

1,5-benzothiazepine derivatives **76b**,**c** in excellent yields [18] (Scheme 16).

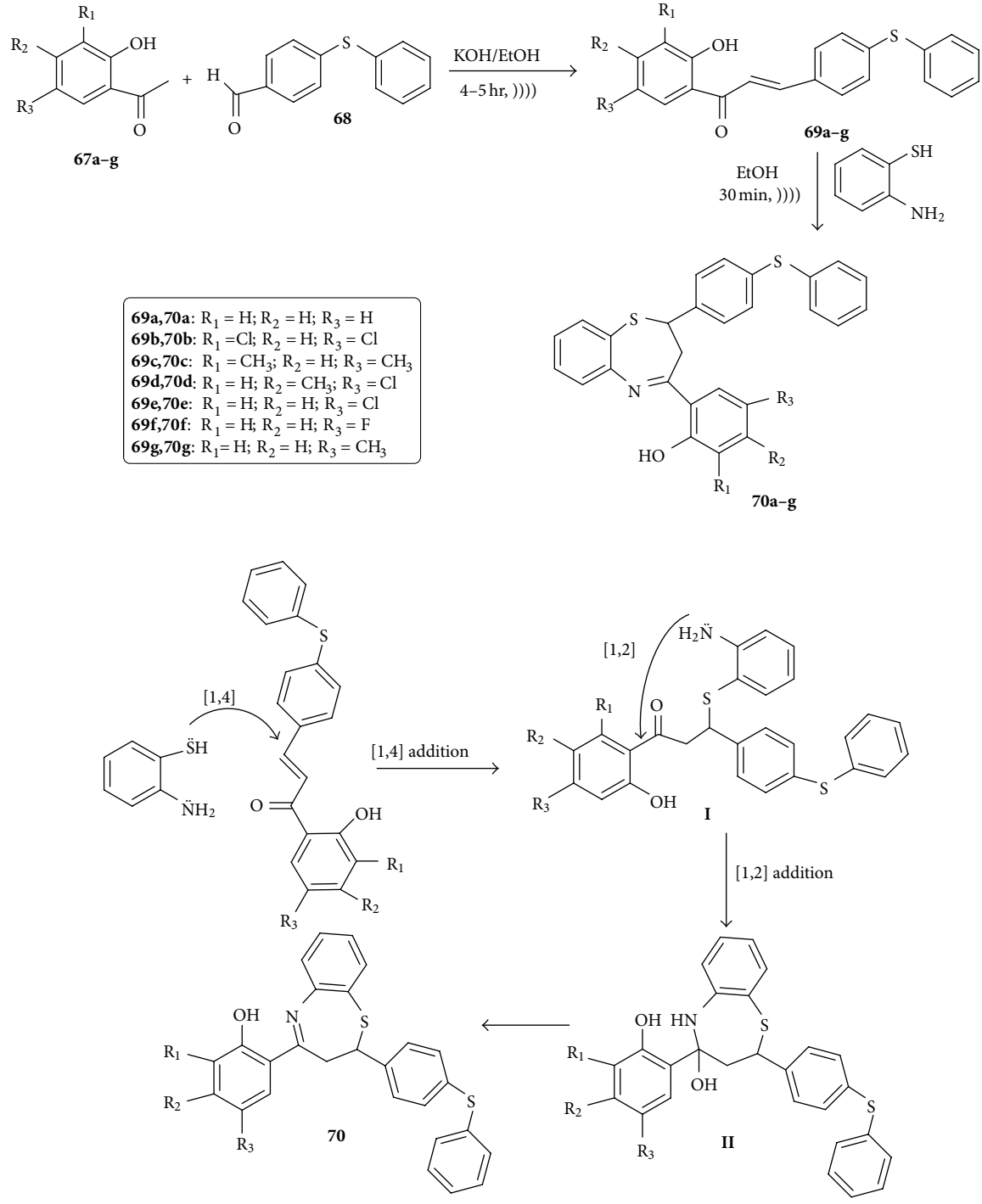
3.1.17. Reaction of Various Hydroxyl Chalcones with o-Aminothiophenol in the Presence of Gallium (III) Triflate. Reactions of *o*-aminothiophenol and the hydroxy chalcones **77a–h** in the presence of water-tolerant strong Lewis acid catalyst $Ga(OTf)_3$ (10 mol%) lead to the 1,5-benzothiazepines **78a–h** in moderate to excellent yields. The *ortho*-OH group of chalcones is crucial for this unprecedented condensation process.

A proposed reaction mechanism involves at first, $Ga(OTf)_3$ catalyst and *o*-hydroxychal-cone **I** form complex **II**, which further reacts with **III** to afford complex **IV** and then **V** after losing H_2O. Then the XH group attacks the C=C bond and lead to the formation of thiazepine **78**. The *o*-hydroxy group in chalcone structure has the following two important roles: (i) it involved in the formation of stable complex **III** by chelating with $Ga(OTf)_3$ and facilitates the dehydration process to from complex **V**; (ii) the presence of this group caused the α,β-unsaturated carbonyl to be more reactive toward the addition of XH [19] (Scheme 17).

3.1.18. Reaction of 4-(4-Fluoro-2-methylphenyl)-4-oxobut-2-enoic Acids with 2-Aminobenzenethiols in the Presence of Lanthanum-Containing Y Zeolite (LaY), While Stirring, under Solventless Conditions. Stirring of *o*-aminothiophenol derivatives and the α,β-unsaturated ketones **79** at room temperature in the presence of Lanthanum-containing Y zeolite (LaY) zeolite catalyst, under solvent less conditions gave 8-substituted-2-carboxy-2,3-dihydro-1,5-benzothiazepines **80a–f** in good to excellent yield. As an initial attempt, a variety of experimental reaction conditions were examined by changing catalyst, reaction medium (MW irradiation, conventional, and stirring), and temperature.

It was found that more acidic LaY zeolite was the best choice of catalyst for the preparation of 2-carboxy-2,3-dihydro-1,5-benzothiazepine **80a**. This can suggest that the acid sites on zeolite work as active sites for this reaction. For checking the catalyst amount's effect on reaction conditions the reaction was tried *via* different amounts of catalyst and 2 g of catalyst amount was sufficient for activation of **80a** product synthesis; higher amount of the catalyst produced lesser yield.

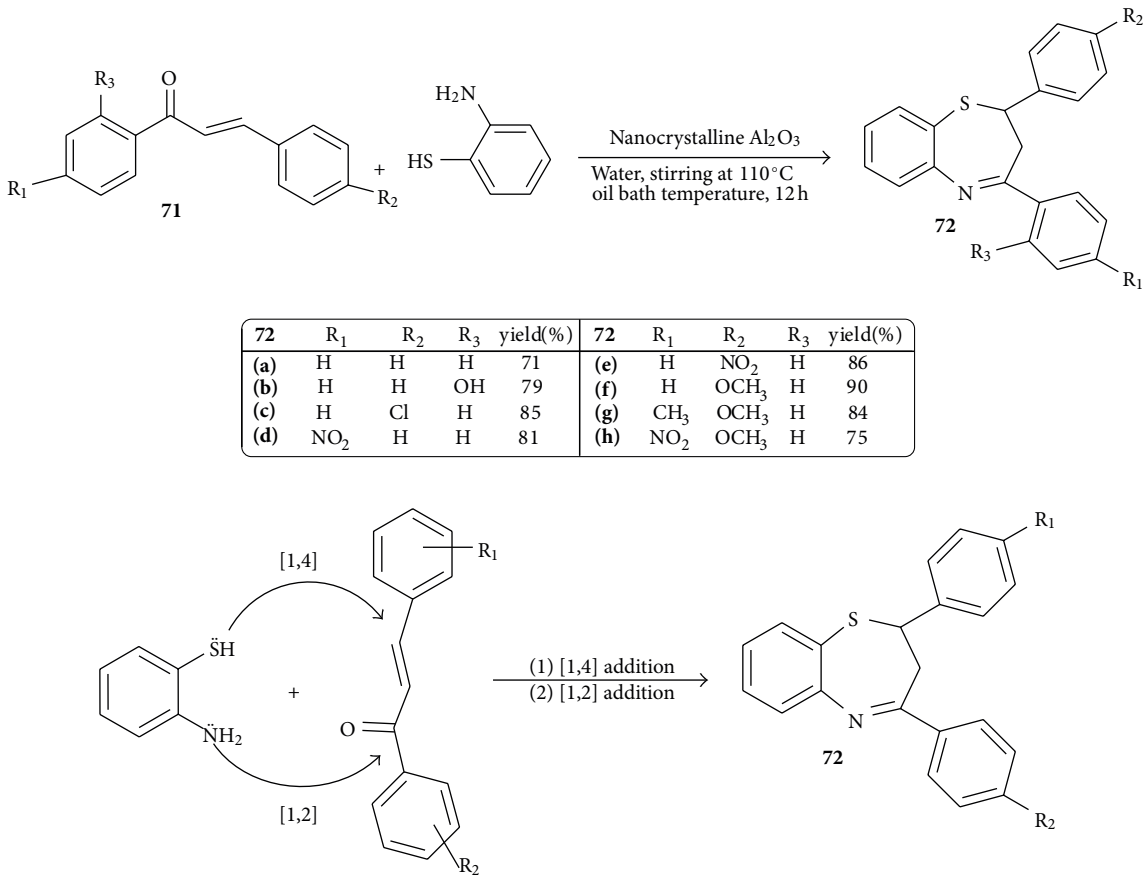
It was also, observed that MW irradiation using different monomode reactor with focused rays and a much more homogeneous electromagnetic field and classical heating gave lower yield with higher reaction time compared to reactions realized under stirring conditions and interphase catalysis. In view of all these observations and results, the other 1,5-benzothiazepines **80b–f** were synthesized *via* reaction of hydroxychalcones **79** and *o*-aminothiophenol using LaY zeolite under stirring at 100°C [20] (Scheme 18).



Proposed mechanism for the construction of the 1,5-benzothiazepine.

Scheme 14: Reaction of 1-(2-hydroxy-3,4,5-trisubstituted-phenyl)-3-(4-(phenylthio)phenyl)prop-2-en-1-ones with *o*-aminothiophenol in ethanol under ultrasonic irradiation *via* a [4 + 3] annulation.

3.1.19. Reaction of 1,3-Diaryl-2-propenones with 2-Aminothiophenol in the Presence of Substoichiometric Amount of Cyanuric Chloride. Cyanuric chloride 2,4,6-trichlorotriazine (TCT) catalyst was employed for preparation of several 1,5-benzothiazepine derivatives *via* reaction of various kinds of 1,3-diaryl-2-propenones **81** with *o*-aminothiophenol. When this reaction was carried out in the absence of cyanuric chloride 2,4,6-Trichlorotriazine (TCT), thin layer chromatography (TLC) and ^{1}H NMR spectra of the reaction mixture showed a combination of starting materials



72	R_1	R_2	R_3	yield(%)	72	R_1	R_2	R_3	yield(%)
(a)	H	H	H	71	**(e)**	H	NO_2	H	86
(b)	H	H	OH	79	**(f)**	H	OCH_3	H	90
(c)	H	Cl	H	85	**(g)**	CH_3	OCH_3	H	84
(d)	NO_2	H	H	81	**(h)**	NO_2	OCH_3	H	75

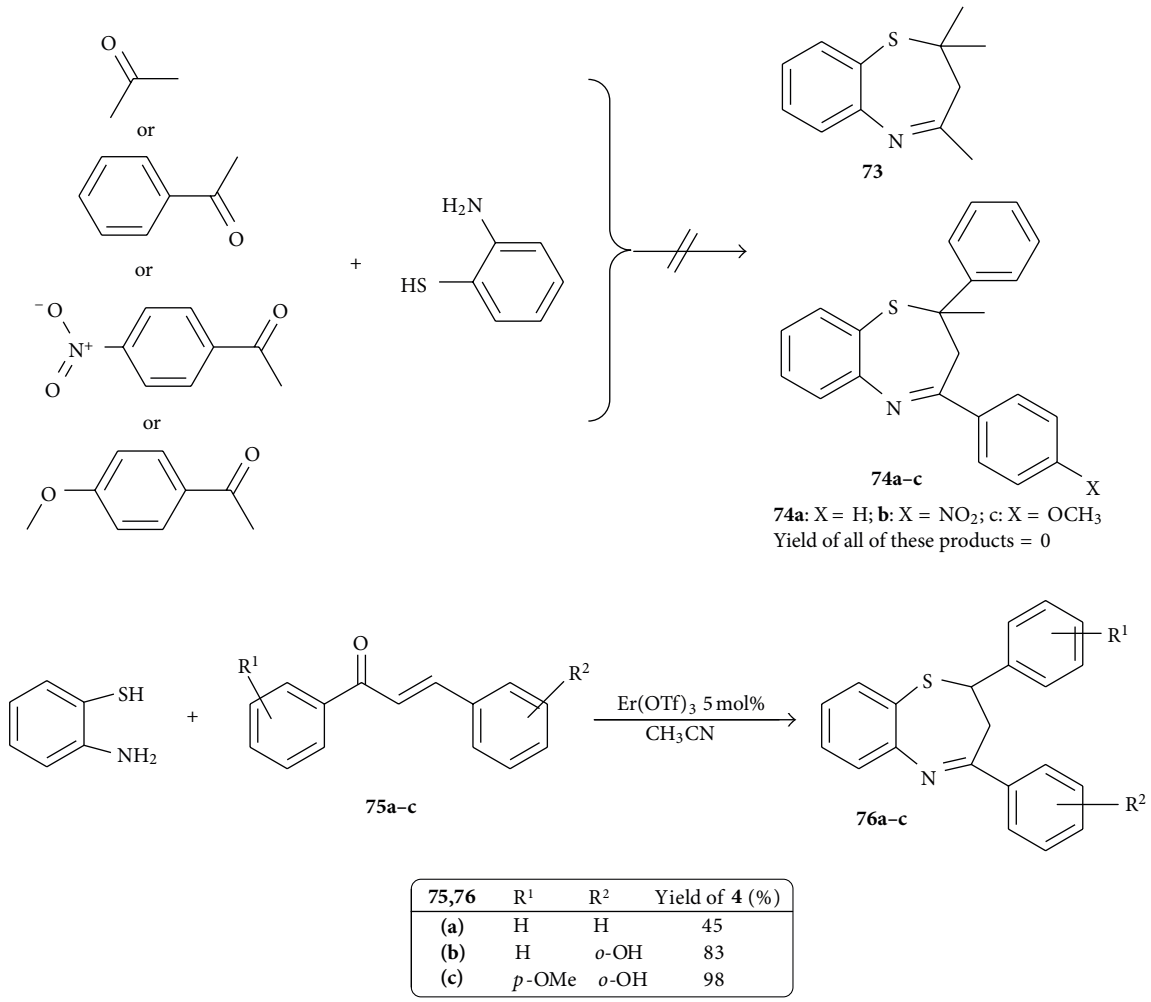
A plausible mechanism for 1,5-benzothiazepines

Scheme 15: Thermal reaction of 1-(2,4-disubstituted-phenyl)-3-(*p*-substituted-phenyl)prop-2-en-1-ones with *o*-aminothiophenol in the presence of a catalytic amount of nanocrystalline Al_2O_3.

and corresponding thia-Michael adducts were formed, the expected benzo[1,5]thiazepines were afforded in very poor yield. Upon repeating the reaction in the presence of TCT catalyst (5 mol%), between 80 and 90°C, the expected benzothiazepine derivatives **82a–l** were obtained in high yield, whether bearing electron-withdrawing groups (such as halide or nitro) or electron-donating groups (such as the alkyl group). It is worthy to note that the *in situ* generated HCl (from cyanuric chloride) efficiently catalyzed the reaction and act as protic acid to activate the carbonyl oxygen for forming a carbo-cation. So, subsequent intramolecular nucleophilic attack by the NH_2 group on the carbo-cation followed by dehydration forms the desired 1,5-benzothiazepines **82**. Also, doing the reaction under dry reaction conditions in the presence of MS 4 Å was met with failure, a matter which indicated that the "incipient" moisture plays an important role for HCl generation *in situ* from TCT catalyst [21] (Scheme 19).

3.1.20. Microwave-Assisted Reaction of 2-Aminothiophenol and 1,3-Substituted-prop-2-en-1-ones in the Presence of Zinc Acetate. One pot efficient facile, solvent-free microwave-assisted green synthesis of 1,5-benzothiazepine derivatives **86** has been approved *via* cyclo-condensation of *o*-aminothiophenol and 1,3-substituted-prop-2-en-1-ones **85a–h** (prepared *via* Claisen-Schmidt condensation of acetophenone or substituted acetophenone **83** or **84** in ethanol in the presence of 40% KOH) *via* using zinc acetate as an eco-friendly catalyst. The thiazepine products **86a–h** were synthesized in shorter reaction time and better yields as compared with their corresponding prepared *via* conventional synthesis (4–6.5 hr; 63–70% yield) [22] (Scheme 20).

3.1.21. Mirowave Irradiation of 1,3-Substituted-prop-2-en-1-one with o-Aminothiophenol in the Presence of Zinc Acetate in Solvent-Free Conditions. Reaction of 1,3-substituted-prop-2-en-1-ones **89a–f** (prepared from acetylated α-naphthol **87** and the corresponding aromatic aldehyde **88** in basic medium) with *o*-aminothiophenol under microwave irradiation for 2-3 minutes at 80–85°C in the presence of eco-friendly catalyst zinc acetate, solvent-free conditions afforded the 1,5-benzothiazepines **90a–f** in good yield and short reaction time. Upon repeating the reaction, using conventional method by mixing of the acetylated α-naphthol with various aldehydes in ethanol in the presence of 40% KOH, heating under reflux for the proper time the benzothiazepine



75,76	R^1	R^2	Yield of **4** (%)
(a)	H	H	45
(b)	H	*o*-OH	83
(c)	*p*-OMe	*o*-OH	98

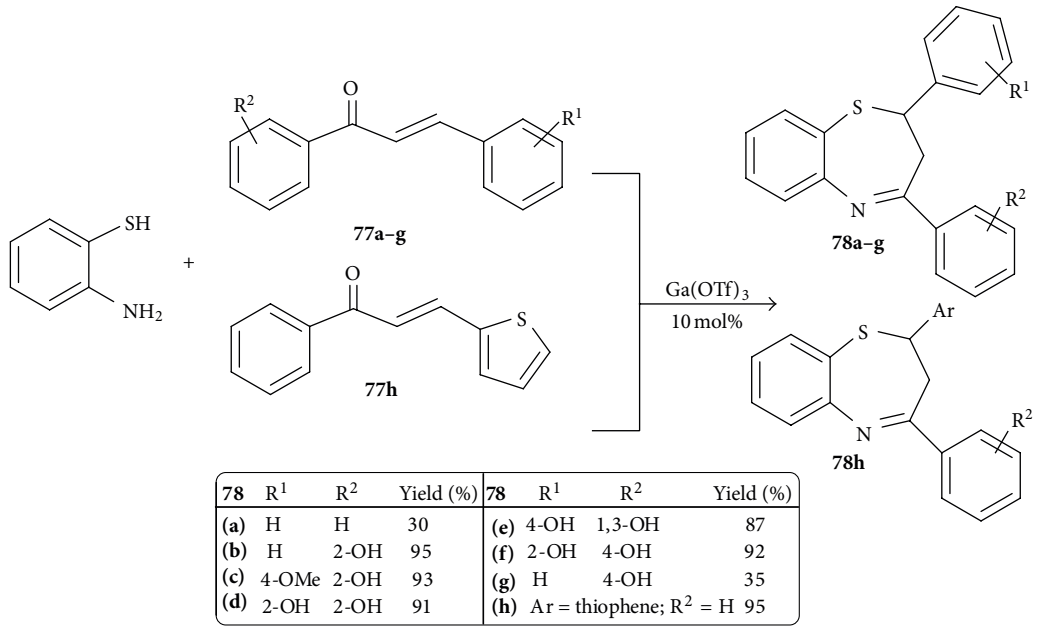
Scheme 16: MW-assisted condensation reactions of *o*-aminothiophenol with carbonyl compounds in presence of erbium (III) triflate.

products **90a–f** were formed in a comparative long reaction time and low yield [23] (Scheme 21).

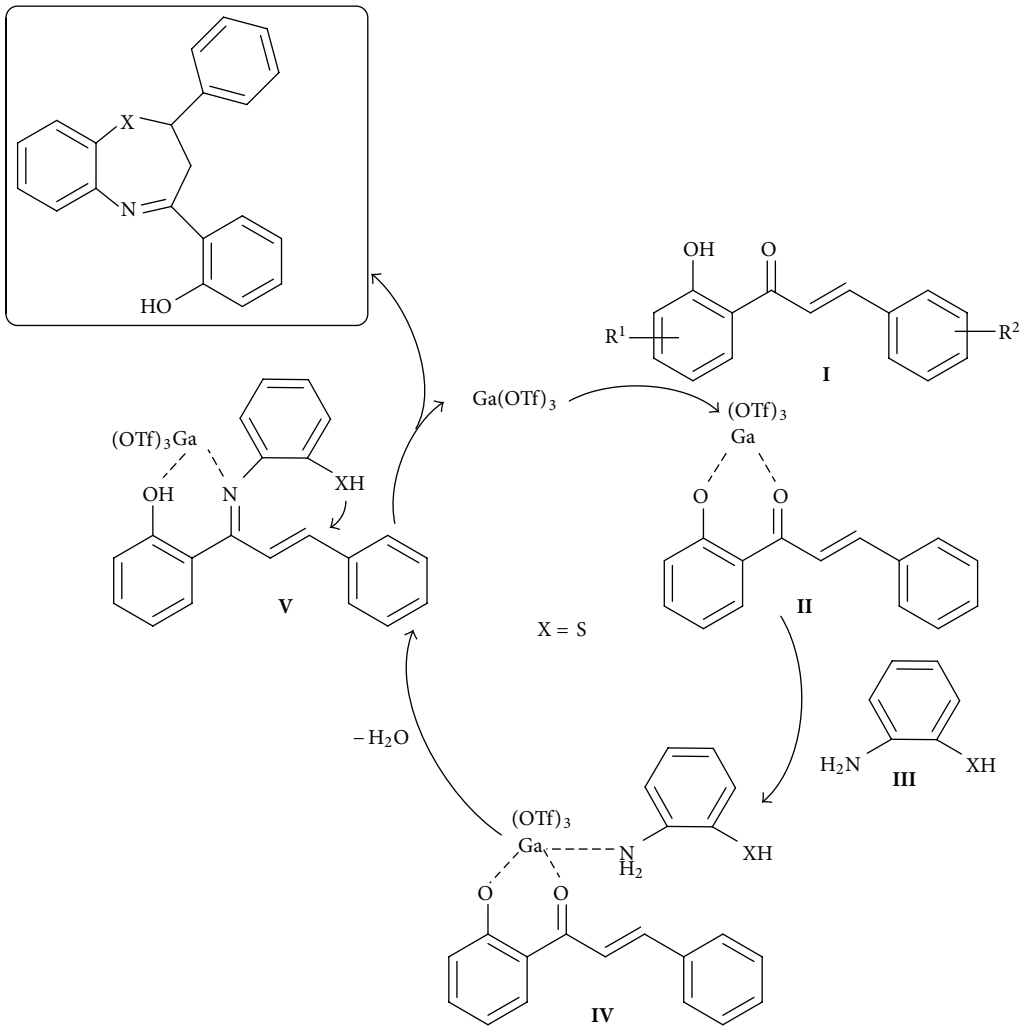
3.1.22. Mannich Condensation Reaction of Substituted 1,8-Naphthyridines and Substituted 2-Aminothiophenols in the Presence of Crystalline $Bi(NO_3)_3{\cdot}5H_2O$ Catalyst under MW Irradiation and Comparison with or without Adding Any Solid Support as Well with Its Performing under Thermal Conditions. The Mannich condensation of substituted 1,8-naphthyridines **91a–d** and substituted *o*-aminothiophenol derivatives in the presence of crystalline $Bi(NO_3)_3{\cdot}5H_2O$ catalyst under Microwave irradiation for about 8-9 min at an interval of 1 min at 160 W gave 1,5-benzothiazepine[7, 6-*b*]-1,8-naphthyridines **92a–j** in good to excellent yields. The reaction proceeds through condensation of amino group with aldehydic group of 1,8-naphthyridines; it is the sulfur atom that reacts with the carbon next to the chlorine at C_2 of 1,8-naphthyridines, which resulted in the desired 1,5-benzothiazepines **92a–j**. For comparison, the reaction was also carried out in presence of different solid support including silica-gel, acidic alumina, basic alumina, neutral alumina, and molecular sieves (5 Å). Also, the reaction was carried out without adding any support under neat condition, which could be expected to be the most economic method. Unfortunately, lower yields (5–56% yield) were obtained. Therefore, the $Bi(NO_3)_3{\cdot}5H_2O$ is the most effective solid for the synthesis of 1,5-benzothiazepine[7, 6-*b*]-1,8-naphthyridines **92a–j**, whereas acidic alumina, basic alumina, neutral alumina, and molecular sieves (5 Å) were ineffective in giving products in good yields.

Moreover, this reaction when performed under reflux (10–12 h) in MeOH as a solvent, the yields were significantly lower than those obtained using the MW method. So, this simple, practical, and very regioselective method for the synthesis of 1,5-benzothiazepine[7, 6-*b*]-1,8-naphthyridines derivatives was presented using the inexpensive, oxygen and moisture-tolerant, and easily available $Bi(NO_3)_3{\cdot}5H_2O$ catalyst [24] (Scheme 22).

3.1.23. Reaction of 3-(Benzo[d][1,3]dioxol-5-yl)-1-(substituted-phenyl)prop-2-en-1-ones with o-Amino-thiophenol in the Presence of Silica Gel at 80°C for 3 h under Solvent-Free Conditions. 3-(Benzo[*d*][1, 3]dioxol-5-yl)-1-(substituted-phenyl)prop-2-en-1-ones **93a–f** on reaction with *o*-aminothiophenol in

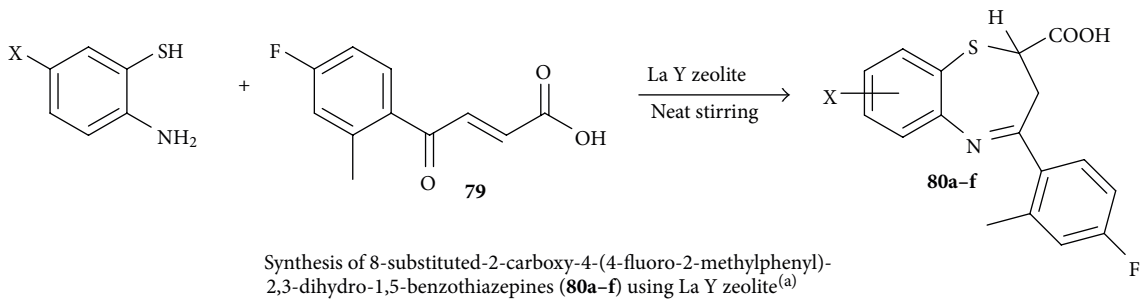


78	R^1	R^2	Yield (%)	78	R^1	R^2	Yield (%)
(a)	H	H	30	**(e)**	4-OH	1,3-OH	87
(b)	H	2-OH	95	**(f)**	2-OH	4-OH	92
(c)	4-OMe	2-OH	93	**(g)**	H	4-OH	35
(d)	2-OH	2-OH	91	**(h)**	Ar = thiophene; R^2 = H		95



Proposed mechanism for $Ga(OTf)_3$-catalyzed reaction of 2-hydroxychalcones with *o*-aminothiophenol.

Scheme 17: Reaction of various hydroxyl chalcones with *o*-aminothiophenol in the presence of gallium (III) triflate.



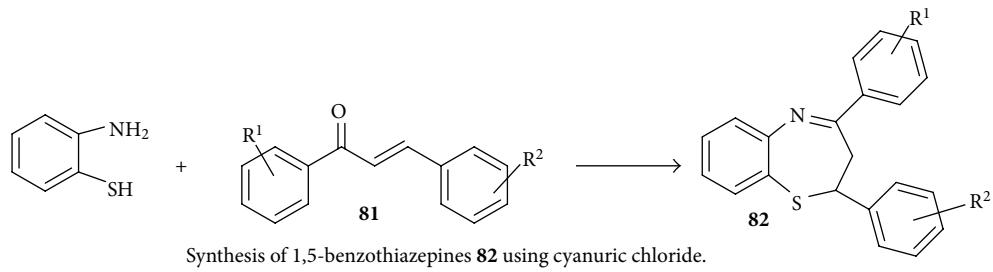
Synthesis of 8-substituted-2-carboxy-4-(4-fluoro-2-methylphenyl)-2,3-dihydro-1,5-benzothiazepines (**80a–f**) using La Y zeolite[a]

80	X	Reaction time (min)	Yield[b](%)
(a)	8-OCH_3	8	94
(b)	8-CH_3	10	75
(c)	8.Cl	12	72
(d)	6-Cl	10	84
(e)	6-Br	13	85
(f)	6-F	15	82

[a] 100 wt % catalyst used that means the substrate catalyst weight ratio is 1 : 1.

[b] Isolated yields.

Scheme 18: Reaction of 4-(4-fluoro-2-methylphenyl)-4-oxobut-2-enoic acids with *o*-amino thiophenol derivatives in the presence of Lanthanum-containing Y zeolite (LaY), while stirring, under solventless conditions.



Synthesis of 1,5-benzothiazepines **82** using cyanuric chloride.

Preparation of 1,3-diaryl-2,3-dihydro-1,5-benzothiazepines **82**[a]

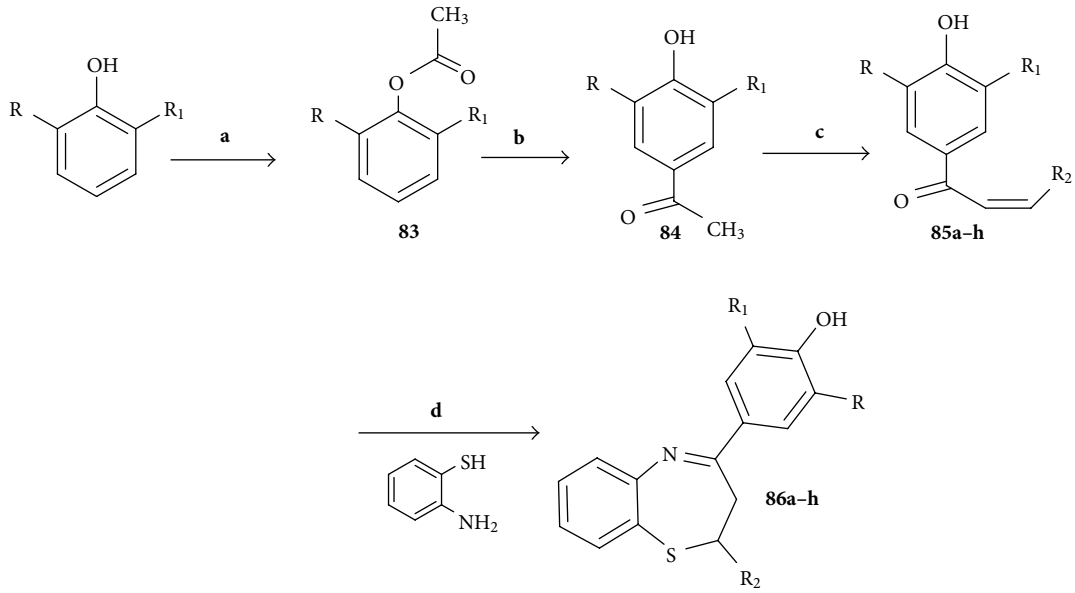
81,82	R^1	R^2	Time (h)	Isolated yield[c] (%) of **82**
(a)	H	H	4	85
(b)	*p*-OCH_3	H	5	83
(c)	*p*-allyloxy	H	5	86
(d)	*p*-OH	H	5	81
(e)	*o*-OH	H	5	80
(f)	H	*p*-OCH_3	3	88
(g)	H	*p*-Cl	3	90
(h)	H	*m*-NO_2	3	91
(i)	*p*-Cl	*p*-OCH_3	5	89
(j)[b]	*p*-Cl	*o*-Cl	5	88
(k)	*o*-OH	Ar =Thinly	6	79
(l)	*o*-OH	*p*-OH	5	82

[a] Reaction conditions: 2aminothiophenol (10 mmol); 1,3-diaryl-2-propenones (10 mmol), TCT (0.5 mmol); 80°C; neat. [b] **82j** is a new product and other thiazepines are known and prepared by other methods.

[c] Isolated yield.

Scheme 19: Reaction of 1,3-diaryl-2-propenones with *o*-aminothiophenol in the presence of sub-stoichiometric amount of cyanuric chloride.

the presence of silica gel at 80°C for 3 h, under solvent-free conditions 2-(benzo[*d*][1, 3]dioxol-5-yl)-4-(substituted-phenyl)-2,3-dihydro-benzo[1, 5]thiazepine derivatives **94a–f** were afforded in good yield. The latter thiazepines probably involves the intermediate [**95**] which was formed by 1,2- and 1,4- type addition of *o*-aminothiophenol with chalcones **93a–f**. The sulfur atom being more nucleophilic in nature than the nitrogen atom attacks the β-carbon of chalcones **93** and gives intermediate [**95**] that easily undergoes dehydration in a nonaqueous medium [25] (Scheme 23).



(**a**) $(CH_3CO)_2O$, 10% NaOH; (**b**) $AlCl_3$ anhyd.; (**c**) R_2CHO, 40% NaOH, MW; (**d**) zinc acetate, MW; R = H, Cl; R_2 = aryl, heteryl

Synthetic routes of the benzothiazepines **86a–h**

MWand conventional synthesis of benzothiazepinens **86a–h**

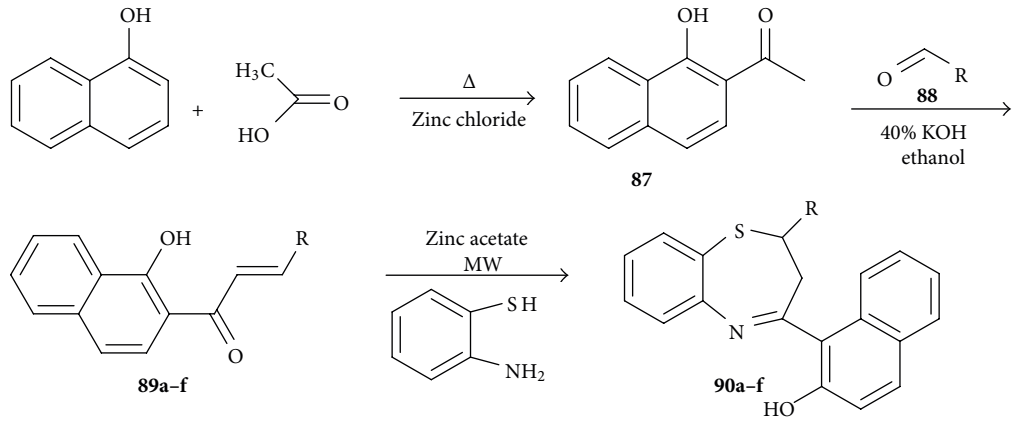
86	R	R_1	R_2	Yield (%)		Time	
				MW	Conv.	MW(min.)	Conv, (hr)
(a)	H	H	*p*-NO_2-Ph	75	69	3.5	4
(b)	H	H	Ph	82	70	3	4.5
(c)	H	H	*o*-NO_2-Ph	70	66	5.5	8
(d)	H	H	*p*-MeO-Ph	65	57	5	6.5
(e)	Cl	Cl	Furyl	65	72	4	6
(f)	Cl	Cl	*p*-MeO-Ph	74	68	3.5	4
(g)	Cl	Cl	Thinly	70	63	5	6.5
(h)	Cl	Cl	*p*-NO_2-Ph	75	70	4	5

Scheme 20: Microwave-assisted reaction of *o*-aminothiophenol and 1,3-substituted-prop-2-en-1-ones in presence of zinc acetate.

3.1.24. Comparative MW Irradiation and Thermal Reactions of β-Benzoyl Arylic Acid with o-Aminothiophenols and Chloroacetyl Chloride over the Basic Alumina as Inorganic Solid Support. β-Benzoyl arylic acid **96** reaction with 5-substituted-*o*-aminothiophenol derivatives and 2-chloroacetyl chloride **98** under MW irradiation over basic alumina (as inorganic solid support) in absence of any solvent occurred in 5-6 min gave only the desired azeto-benzothiazepines **99** in excellent yield.

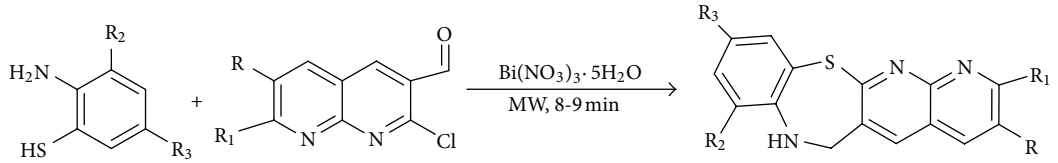
The basicity of alumina is sufficient to cause this cycloaddition reaction and the 1,5-benzothiazepines **97** were formed *in situ*, as intermediates, by reaction of β-benzoyl arylic acid **96** and 5-substituted *o*-aminothiophenol derivatives under MW irradiation.

When a solution of Et_3N in benzene was added drop wise into a solution of 2-chloroacetyl chloride and 1,5-benzothiazepine **97** in benzene mixture of azeto[2, 1-*d*][1, 5]-benzothiazepines **99**, the ring contracted 2-substituted 2,3-dihydro-3-phenyl-*N*-acetyl-2-styrylbenzothiazole **100** was obtained in fair yields. Presumably, the low yield of azeto-[2, 1-*d*][1, 5]benzothiazepine **99** is due to the competitive ring contraction with "Staudinger reaction" under the reaction conditions. The yield could be improved to 30% if a solution of 2-chloroacetyl chloride **98** in benzene was added drop wise into a solution of benzothiazepine and Et_3N in benzene. Although the ring contraction could be inhibited under this additional mode, the yield of **99a** was still low when 1.5 equivalents of **98** were used and a new byproduct **101** was obtained. Upon applying 3.0 equivalents of **98** to improve the yield, the desired azeto[2, 1-*d*][1, 5]benzothiazepines **99** were not obtained, but the yield of the by-product **101** was improved slightly. Another trial involved first the formation of diketenes through addition of Et_3N to a solution of **98** in benzene and subsequent addition of the 1,5-benzothiazepine **99a** into the resulting reaction mixture which resulted only in the 1,3-oxazine derivative **101** in low yield. On the other hand, under microwave irradiation the desired azeto[2, 1-*d*][1, 5]-benzothiazepine **99a** was formed as the only product with



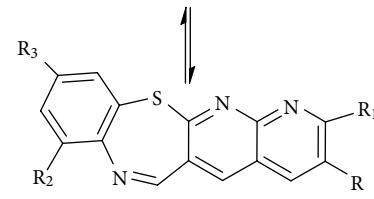
90	R	Yield (%)		Time	
		MW	Conv.	MW(min.)	Conv. (hrs)
(a)	C_6H_5	72	65	2.5	5
(b)	*o*-OHC_6H_4	88	80	1	2
(c)	*p*-ClC_6H_4	78	67	1.5	5.5
(d)	*p*-$OCH_3C_6H_4$	61	59	1	2.5
(e)	Furyl	70	67	2	3
(f)	Thinyl	60	58	3	4

Scheme 21: Mirowave irradiation of 1,3-substituted-prop-2-en-1-one with *o*-aminothiophenol in presence of zinc acetate in solvent-free conditions.



91a–d

92	92
(a) R = R_1= R_2 = R_3 = H	**(f)** R_2 = CH_3, R = R_1 = R_3 = H
(b) R = CH_3, R_1 = R_2 = R_3 = H	**(g)** R_3 = CH_3, R = R_1 = R_2 = H
(c) R = OCH_3, R_1 = R_2 = R_3 = H	**(h)** R = CH_3, R_1 = R_3 = H, R_2 = CH_3
(d) R_1 = CH_3, R = R_2 = R_3 = H	**(i)** R_2 = Cl, R = R_1 - R_3 = H
(e) R = Cl, R_1 = R_2 = R_3 = H	**(j)** R_3 = Cl, R = R_1 = R_2 = H



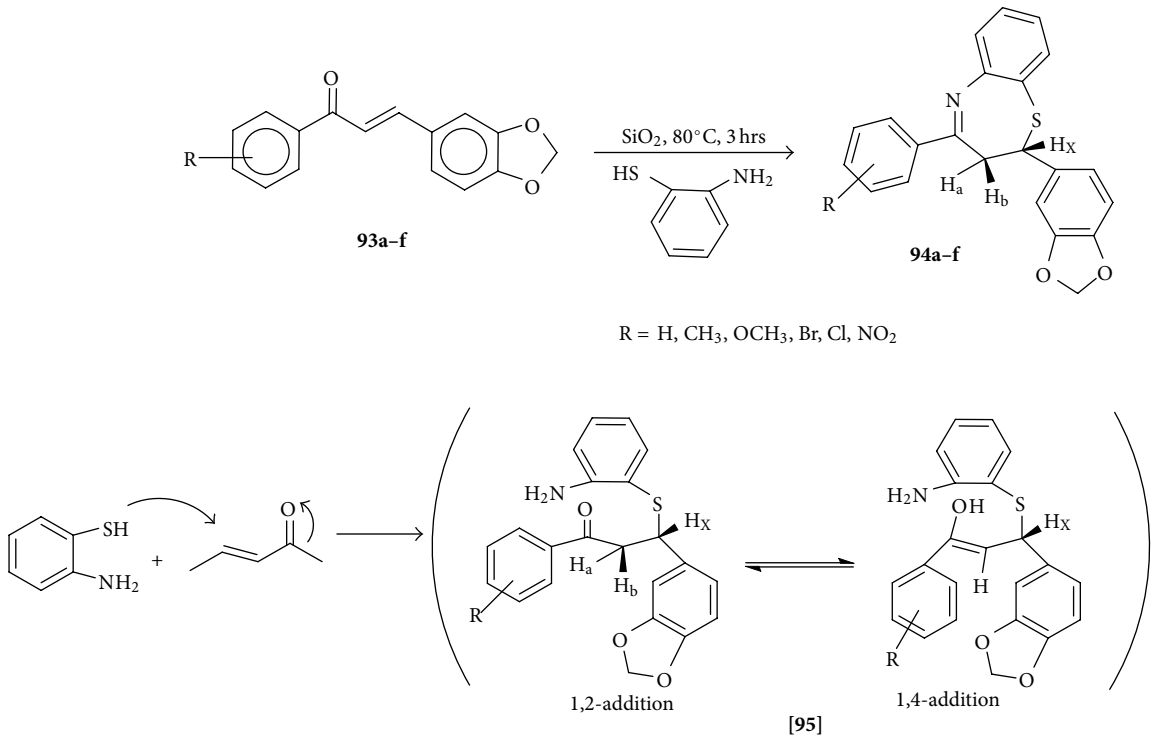
92a–j

Scheme 22: Mannich condensation reaction of substituted 1,8-naphthyridines and substituted *o*-aminothiophenols in the presence of crystalline $Bi(NO_3)_3{\cdot}5H_2O$ catalyst under MW irradiation and comparison with or without adding any solid support as well as with its performance under thermal conditions.

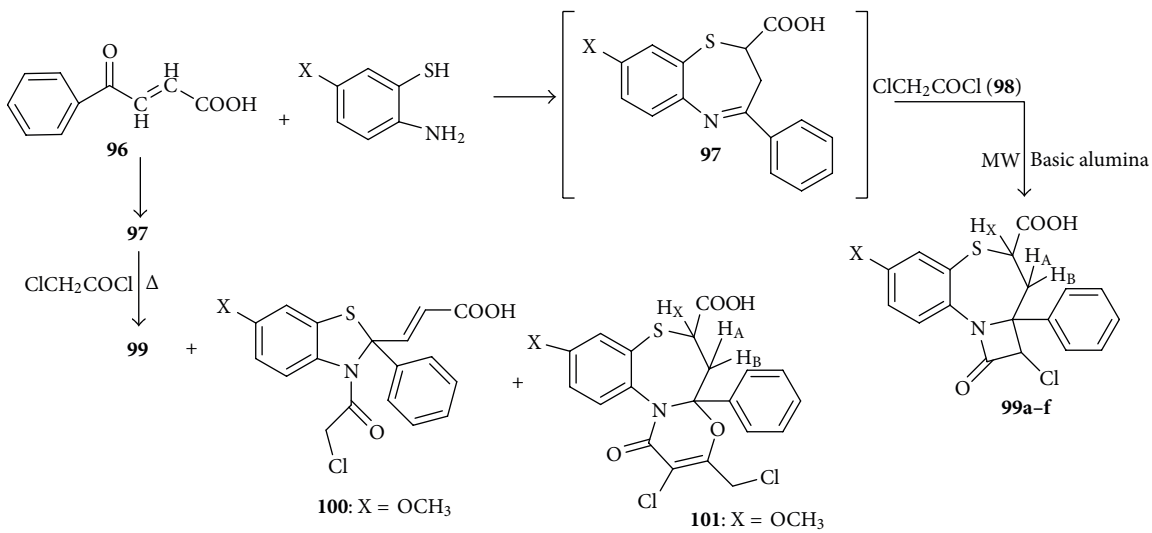
good yield. Similarly, products **99b–f** were obtained in fair to good yield [26] (Scheme 24).

3.1.25. Thermal (Short Time) Reaction of 1-Methyl-3,5-bis-(arylidene)-4-piperidones with o-Aminothiophenol in the Presence of a Catalytic Amount of Acetic Acid under Atmospheric Pressure. MW irradiation of *o*-aminothiophenol and 1-methyl-3,5-bis-(arylidene)-4-piperidones **102** (1 : 1 molar ratio) in the presence of CH_3COOH as a catalyst in silica bath (~85°C) under atmospheric pressure for 4–10 min afforded 2-methyl-11-aryl-4-[(*E*)-arylmethylidene]-1,2,3,4,11,11-a hexahydropyrido[3, 4-*c*][1, 5]benzothiazepines **103** in excellent yield. The same reaction in either C_2H_5OH or MeOH at reflux with few drops of CH_3COOH took several hours with less than 30% conversion, while refluxing in CH_3COOH alone led to complete decomposition of the reaction mixture [27] (Scheme 25).

3.1.26. Thermal Reaction of (E)-3-(3,4-Disubstituted-phenyl)-1-(2-hydroxy-3,4,5-trisubs-tituted-phenyl)prop-2-en-1-ones with 2-Aminothiophenol under the Influence of Glacial Acetic Acid. Oxidative cyclisation of 3-(3,4-di-substituted-phenyl)-1-(2-hydroxy-3,4,5-tri-substituted phenyl)prop-2-en-1-ones **104a–j** (prepared *via* Claisen-Schmidt condensation of



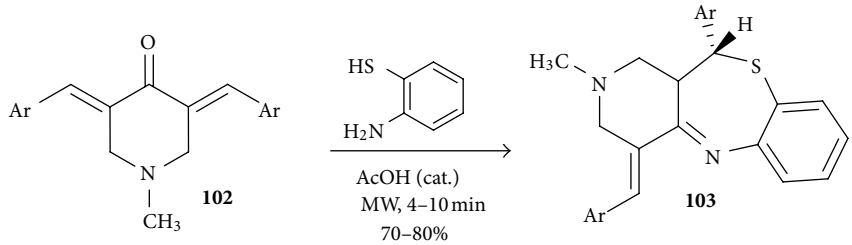
Scheme 23: Reaction of 3-(benzo[*d*][1, 3]dioxol-5-yl)-1-(substituted-phenyl)prop-2-en-1-ones with *o*-aminothiophenol in the presence of silica-gel at 80°C for 3 h under solvent-free conditions.



99	X	Time[(a)] (min)	Yield (%)
(a)	OCH_3	12 + 3	90
(b)	CH_3	10 + 5	87
(c)	Cl	12 + 6	83
(d)	Br	10 + 5	86
(e)	CF_3	9 + 4	88
(f)	F	10 + 5	87

[(a)] Time (12 + 3) indicates first irradiation for 12 min. gives compound **97** (detected by TLC) and then further irradiation after adding chloroacetyl chloride for 3 min yields **99a**

Scheme 24: Comparative MW irradiation and thermal reactions of β-benzoyl arylic acid with *o*-aminothiophenols and chloroacetyl chloride over the basic alumina as inorganic solid support.



Synthesis of [1,5] benzothiazepines **103.**

Synthesis of [1,5] benzothiazepines **102** and **103**

Ar **102** or **103**	**102)**	MW method		Conventional method		**103**	Yield [(b)] (%)
		Time (min)	Yield [(a)] (%)	Time (min	Yield (%)		
(a) Ph	**(a)**	6	80	10	30	**a)**	94
(b) 4 -Cl-Ph	**(b)**	8	79	10	28	**b)**	96
(c) 4-Me-Ph	**(c)**	8	75	10	25	**c)**	95
(d)4-MeO-Ph	**(d)**	8	70	10	21	**d)**	98
(e) 4-F-Ph	**(e)**	10	70	11	23	**e)**	95
(f) 3-F-Ph	**(f)**	4	80	10	27	**f)**	96
(g) 2-Cl-Ph	**(g)**	6	72	10	25	**g)**	95
(h) 2-MePh	**(h)**	8	75	11	24	**h)**	96
(i) 2-Thienyl	**(i)**	6	80	11	26	**i)**	94
(j) 1-Naphthyl	**(j)**	6	75	10	25	**j)**	97

[(a)] Yield after recrystallisation., [(b)] Yield after column purification

Scheme 25: Thermal (short time) reaction of 1-methyl-3,5-bis-(arylidene)-4-piperidones with *o*-aminothiophenol in the presence of a catalytic amount of acetic acid under atmospheric pressure.

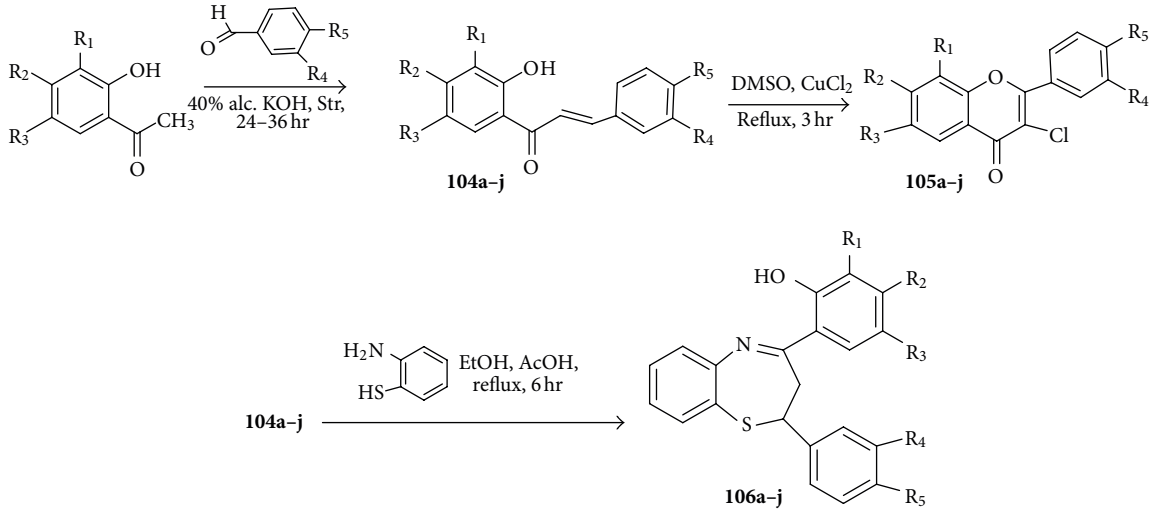
various substituted acetophenones with aromatic aldehydes in the presence of EtOH/KOH) using $CuCl_2$ at reflux in DMSO gave 3,6-dichloro-2-(4-fluorophenyl)-7-methyl-4*H*-chromen-4-one **105a–j** in good yield. The chalcones **104a–j** on treatment with *o*-aminothiophenol at reflux condition in EtOH under the influence of glacial CH_3COOH for 6 h afforded the 1,5-benzothiazepines **106a–j** in good yield [28] (Scheme 26).

3.1.27. Intramolecular Cyclisation of 3-((2-Amino-4-pheny/substituted-phenyllthio)(phe-nyl)methyl)pentane-2,4-diones or -hexane-2,4-diones Followed by Dehydration in Acetic Acid/Methanol. Knoevenagel condensation of selected aromatic aldehydes with 2,4-pentanedione in dry benzene catalyzed by piperidine gave 3-arylidenepentane-2,4-dione derivatives **109**. Michael addition of *o*-aminothiophenol derivatives to **109** yielded the corresponding 3-(2-amino-4-pheny/substituted-phenyllthio)(phenyl)methyl)-pentane-2,4-diones **110**.

Intramolecular cyclisation of **110**, followed by dehydration in a CH_3COOH/MeOH provided 1,5-benzothiazepines **107a–r** in fair yield. The target 2,5-dihydro-2-aryl-3-ethoxycarbonyl-4-methyl-1,5-benzothiazepines **108a–d** were prepared in 20–33% yield through the same reaction sequence starting from the hexane-2,4-diones **111**. It is worth noting that when 4-hydroxybenzaldehyde was used as the starting material, compound **108e** was obtained as the final product in 20% yield, whose structure had an unusual imine (–N=C–C–) rather than enamine (–N–C=C–), as demonstrated by its ^{1}H NMR spectrum [29] (Scheme 27).

3.1.28. Thermal Reaction of Methylene-bis-chalcones with o-Aminothiophenol in Ethanol in the Presence of Acetic Acid. Condensation of 5-(3-formyl-4-hydroxybenzyl)-2-hydroxybenzaldehyde **112** with methyl ketones in the presence of aqueous KOH (60%) at room temperature afforded methylene-bis-chalcones **113**. The latter chalcones on reaction with *o*-aminothiophenol, in EtOH in the presence of CH_3COOH at reflux for 4 h, gave methylene-bis-[1, 5]-benzothiazepine derivatives **114a–g** in good to excellent yields. The thiazepines **114a–g** on condensation with α-bromoacetophenone, in the presence of anhydrous K_2CO_3/dry acetone and catalytic amount of KI, followed by cyclization in ethanolic KOH, gave methylene-bisbenzofurano-[1, 5]-benzothiazepine derivatives **115a–g** (yield% was not reported) and were purified by column chromatography using silica-gel (60–120 mesh)/petrol ether (60–80°C) [30] (Scheme 28).

3.1.29. Reaction of Exocyclic α,β,γ,δ-Unsaturated Ketones with o-Aminothiophenol in a Mixture of Boiling Toluene and Acetic Acid. The exocyclic $\alpha,\beta,\gamma,\delta$-unsaturated ketones **116–123** when allowed to react with *o*-aminothiophenol in a mixture of boiling toluene and CH_3COOH the tetracyclic 1,5-benzothiazepines **124–131** were obtained in relatively good to medium yields (59–71%). Neither the yield nor course of the reaction was influenced by the presence of an electron donor or an electron acceptor *o*-substituent in the starting material. Replacement of the styryl group by a 2-(furan-2-yl)ethenyl-one slightly enhanced the yield of the formation of 1,5-benzothiazepines **130** and **131** (71 and 68% resp.) [31] (Scheme 29).



Charcterization data of comps **105a–j** and **106a–j**

105,106	R_1	R_2	R_3	R_4	R_5	Yield (%) of **105**	Yield (%) of **106**
(a)	H	H	H	H	F	59	70
(b)	H	H	CH_3	H	F	58	63
(c)	H	H	Cl	H	F	60	66
(d)	Cl	H	Cl	H	F	64	71
(e)	H	CH_3	Cl	H	F	61	69
(f)	H	H	H	OCH_3	OCH_3	60	70
(g)	H	H	CH_3	OCH_3	OCH_3	57	58
(h)	H	H	Cl	OCH_3	OCH_3	59	62
(i)	Cl	H	Cl	OCH_3	OCH_3	60	66
(j)	H	H	H	H	F	55	62

Scheme 26: Thermal reaction of (*E*)-3-(3,4-disubstituted-phenyl)-1-(2-hydroxy-3,4,5-trisubstituted-phenyl)-prop-2-en-1-ones with *o*-aminothiophenol under the influence of glacial acetic acid.

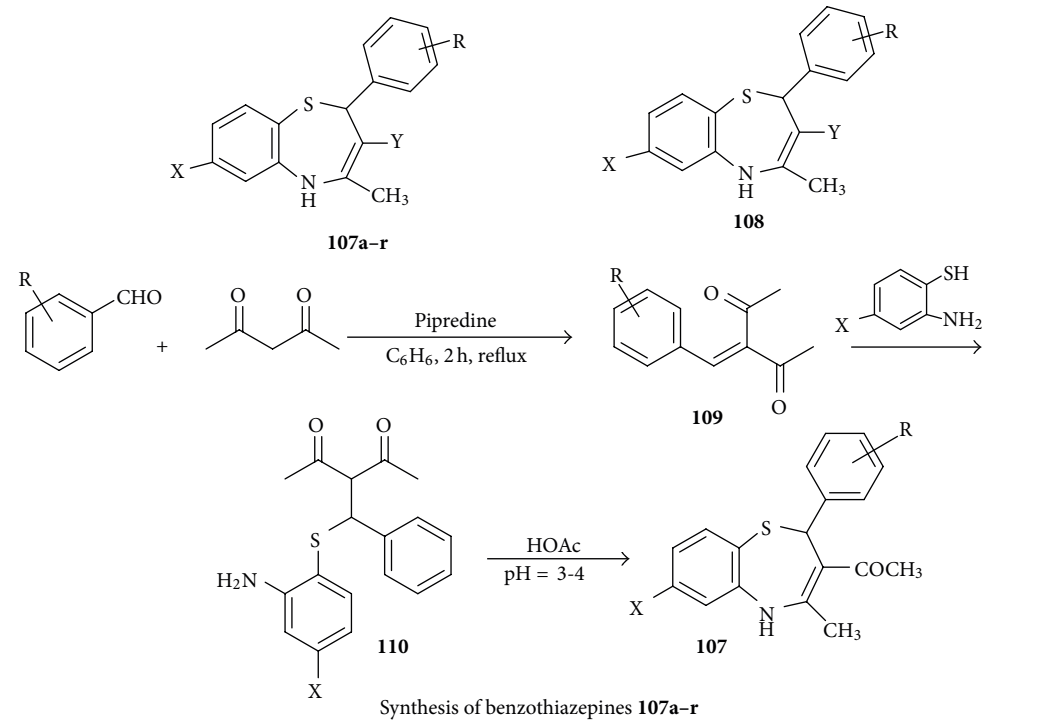
3.1.30. Reactions of Thienylidene Malononitrile and o-Aminothiophenol in the Presence of Catalytic Amount of Piperidine. *o*-Aminothiophenol and thienylidene malononitrile **132** (equimolecular ratios) upon heating under reflux in EtOH containing piperidine for 30 min gave 2-amino-3-cyano-4-(2-thienyl)[1, 5]benzothiazepine **135** in good yield. Formation of **135** may proceed *via* the intermediate (**133**) which cyclized to afford the intermediate (**134**). The latter intermediate in turn tautomerized to 2-amino-4,5-dihydrobenzothiazepine and released hydrogen under an aerobic oxidation to give **135**. The latter thiazepine when reacted with ethyl cyanoacetate **136a** and diethyl malonate **136b** in CH_3COOH afforded pyridobenzothiazepine derivatives **138a**,**b**. Elimination of ethanol from the acetate group gave the intermediate (**137**), subsequently cyclized *via* the addition of active methylene hydrogens to the cyano function yielding 4-amino-5-[2-thienyl]pyrido[6, 5-*b*][1, 5]benzothiazepine-1, 2-dihydro-2-one derivatives **138a,b**. To confirm the structure of type **138**, compound **138b** ($X = CO_2C_2H_5$) on boiling at reflux with hydrazine hydrate in ethanolic piperidine solution gave the pyrazolo[3, 4 : 4′, 3′]pyrido[6, 5-*b*]benzothiazepine derivatives **139** in satisfactory yield. Similarly, the azepine **135** reacted with malononitrile **140a** and cyanothioacetamide **140b** in acetic acid at a reflux temperature to give in each case the same product **141**. In the case of malononitrile **140a** 2 successive steps of a nucleophilic addition to the cyano functions yield **141**; whereas in case of **140b**, a condensation between the thione group of the amide and the amine of **135** released hydrogen sulfide was followed by a nucleophilic addition of the active methylene to the cyano function affording the same final product **141**.

Also, reaction of **135** with arylidene malononitrile **142a–c** afforded pyrido-benzothiazepine derivatives **146a–c**. Formation of the latter thiazepines was explained *via* the intermediate (**143**), which cyclized *via* a nucleophilic addition of hydrogen of arylidene to a cyano function of benzothiazepine to form dihydropyridine intermediate (**144**). The latter released hydrogen cyanide to give **145** and tautomerized to form the final product **146**.

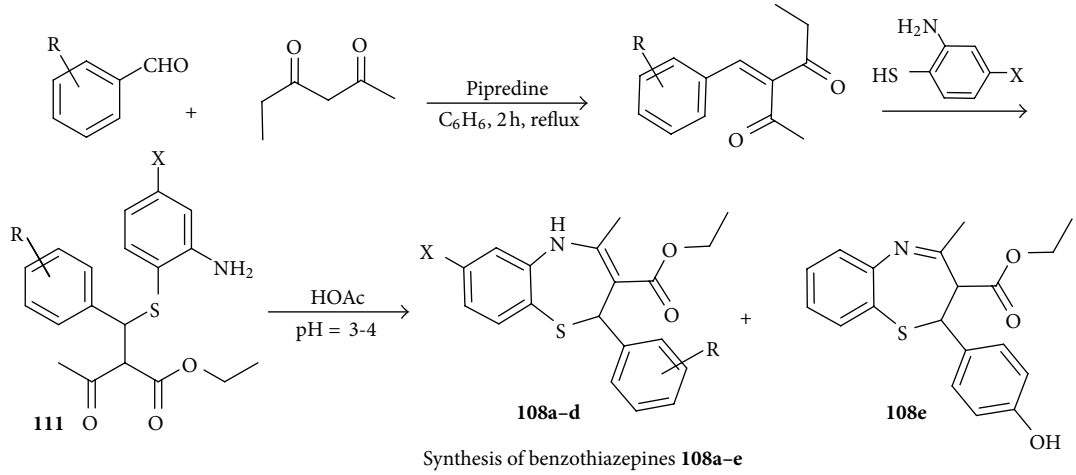
Moreover, Compound **135** reacted easily with urea in AcOH to afford 2,4-diaminopyrimidobenzothiazepine **147** (65% yield) *via* cyclo-condensation addition reaction.

Furthermore, reaction of **135** under reflux with triethylorthoformate yielded the ethoxymethylidenamino derivatives **148** (61% yield), which on reaction with hydrazine hydrate afforded the corresponding pyrimidobenzothiazepine **149** (60%) *via* the elimination of ethanol followed by a nucleophilic addition to the cyano function.

Finally, the benzothiazepine **135** in EtOH reacted with trichloroacetonitrile to give benzothiazepine **153** (60% yield). Compound **153** was suggested to be formed *via* the intermediate (**150**) which in turn cyclized to the pyrimidine



Synthesis of benzothiazepines **107a–r**



Synthesis of benzothiazepines **108a–e**

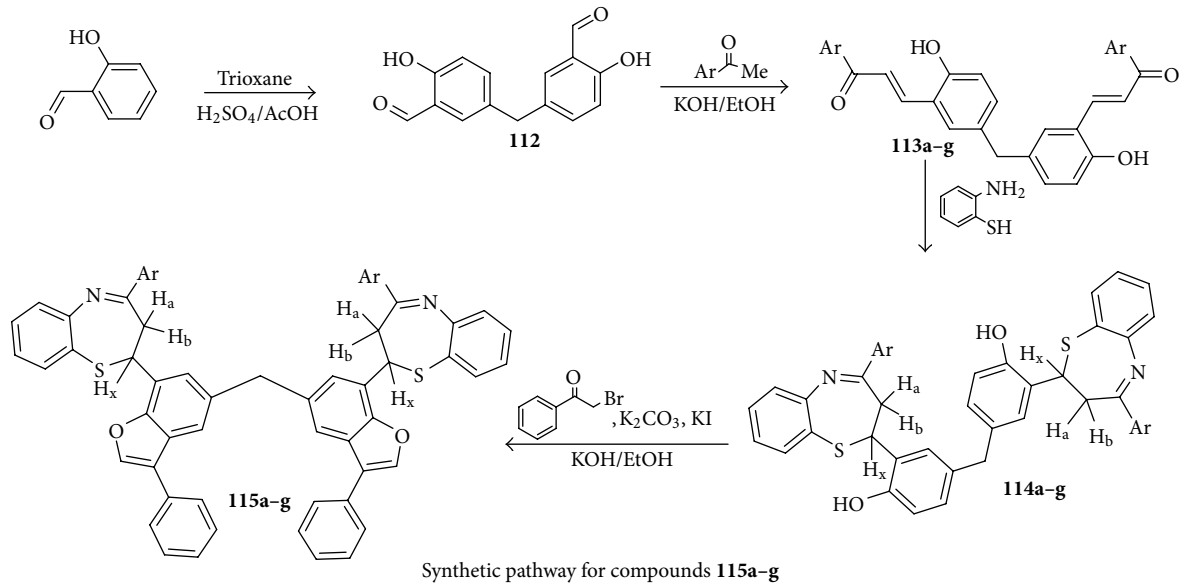
107 R	R	R
(a) *p*-NO_2	**(g)** H	**(m)** *p*-Cl
(b) *o*-NO_2	**(h)** *p*-OCH_3	**(n)** *o*-Cl
(c) *p*-Cl	**(i)** *p*-F	**(o)** H
(d) *o*-Cl	**(j)** 2,4-dichloro	**(p)** *p*-F
(e) *p*-CH_3	**(k)** *p*-NO_2	**(q)** *p*-Br
(f) *p*-OH	**(l)** *o*-NO_2	**(r)** 2,4-dichloro
107a-j: X = H, Y = $COCH_3$		
107k-r: X = Cl , Y = $COCH_3$		

108a-d: X =H, Y = $COOCH_2CH_3$
(a): R = *p*-CH_3
(b): R = *p*-F
(c): R = *p*-NO_2
(d): R = *o*-Cl
108e: X =H, Y = $COOCH_2CH_3$, R = *p*-OH

Scheme 27: Intramolecular cyclisation of 3-((2-amino-4-pheny/substituted-phenyllthio)-(phenyl)methyl)pentane-2,4-diones or -hexane-2,4-diones followed by dehydration in acetic acid/methanol.

intermediate (**151**). In the reaction medium the C-2 of pyrimidine became relatively positive, easily accepted the hydroxide ion from water of intermediate (**152**) yielding the final benzothiazepine **153** (60% yield) [32–36] (Scheme 30).

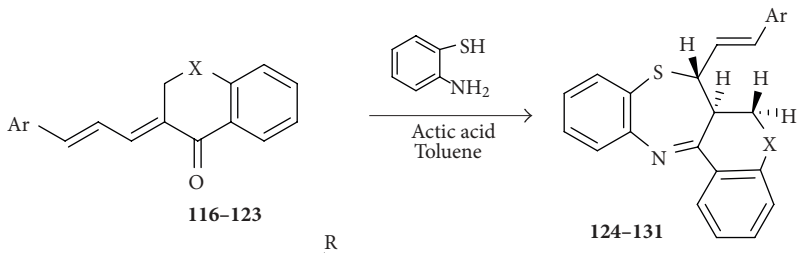
3.1.31. Reaction of 3-[1-oxo-3-(Substituted phenyl)-2-propenyl]-2H-1-benzopyran-2-ones with o-Aminothiophenol in the Prescence of Piperidine. The chalcones **155a–g** (derived from 3-acetyl coumarin derivatives **154** and the proper



Synthetic pathway for compounds **115a–g**

Ar	Ar
(a) C_6H_5	**(e)** 4-NO_2-C_6H_4
(b) 4-Br-C_6H_4	**(f)** 2-furyl
(c) 4-Cl-C_6H_4	**(g)** 2-pyridyl
(d) 4-MeO-C_6H_4	

Scheme 28: Thermal reaction of methylene-bis-chalcones with *o*-aminothiophenol in ethanol in the presence of acetic acid.



Ar: **116–121, 124–129** =

Ar: **122, 123, 130, 131** =

116, 124: X = O, R = H
117, 125: X = O, R = MeO
118, 126: X = O, R = NO_2

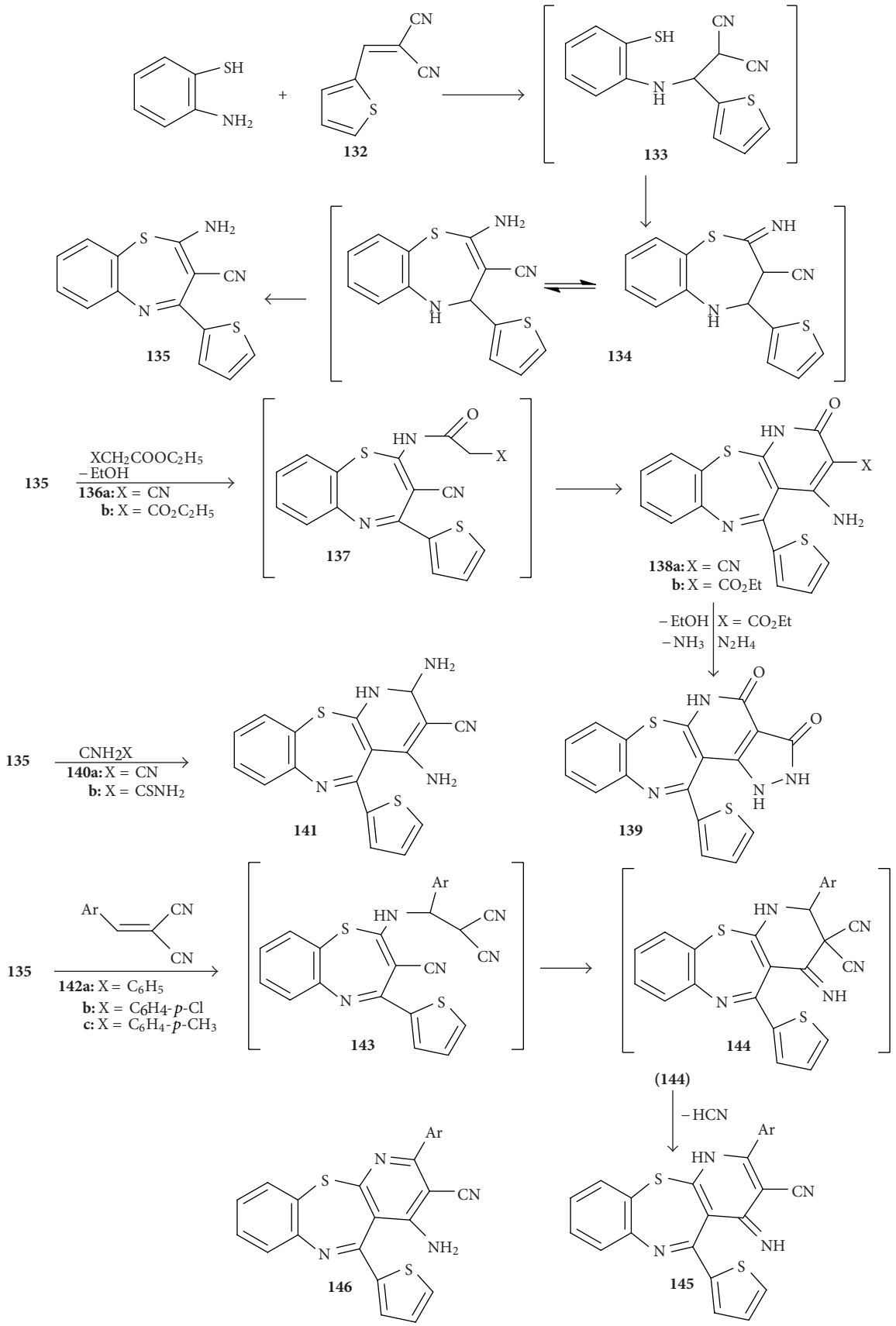
119, 127: X = S, R = H
120, 128: X = S, R = MeO
121, 129: X = S, R = NO_2

Scheme 29: Reaction of exocyclic $\alpha,\beta,\gamma,\delta$-unsaturated ketones with *o*-aminothiophenol in a mixture of boiling toluene and acetic acid.

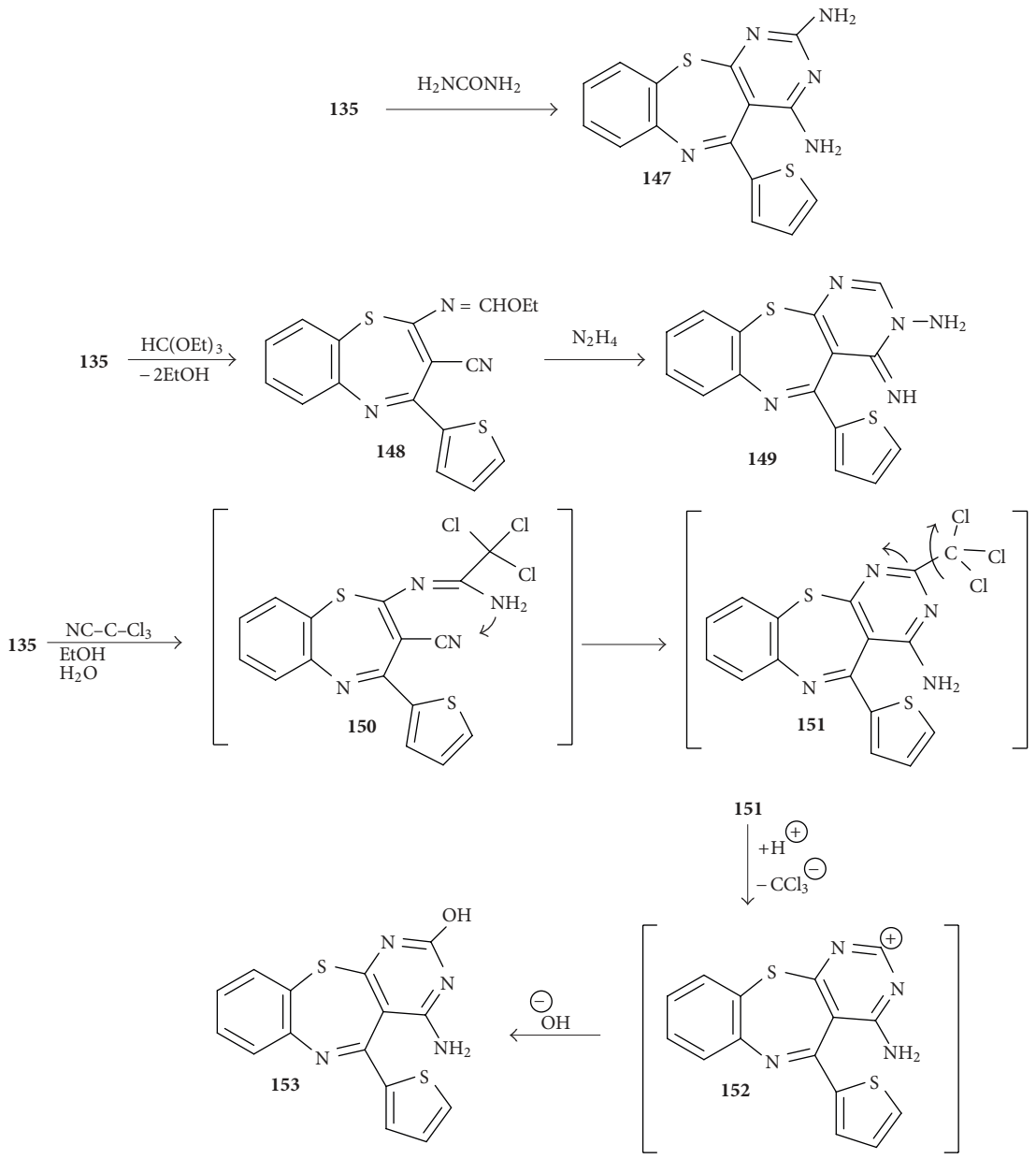
aromatic aldehydes) when reacted with *o*-aminothiophenol in a mild acidic medium using weakly acidified ethanol gave 2-aryl-4-(2*H*-2-oxo-[1]-benzopyran-3-yl]-2,3-dihydro-1,5-benzothiazepines **156a–j** in good to excellent yields. Meanwhile, upon heating the chalcones **155** under reflux in ethanol containing *o*-aminothiophenol and piperidine, the corresponding 2-aryl-4-[2*H*-2-oxo-[1]benzopyran-2-one-3-yl]-2,5-dihydro-1,5-benzothia-zepines **157a–g** were obtained in good yield [37] (Scheme 31).

3.1.32. Reactions of Butoxy(trifluoromethyl)enone with o-Aminophenol or o-Amino-thiophenol Derivatives. Reactions of *t*-butoxy(trifluoromethyl)enones **158** with 1,2-diamines (*o*-phenylene diamine or 1,2-ethylenediamine) lead to 1,5-diazepines **159** and **160**. In comparison, reaction of **158** with *o*-aminophenol derivatives or *o*-aminothiophenol, yielded 1,5-oxazepines or 1,5-thiazepines of type **161**. Good results were obtained by using microwave irradiation. Meanwhile, upon carrying the same reaction in boiling xylene, the condensation leads to a mixture of products [38] (Scheme 32)

3.1.33. Mirowave-Assisted Irradiation of o-Aminobenzenethiol and the Oxirane-2-carboxylate. A diastereo-selective reaction of *o*-aminothiophenol and the oxirane-2-carboxylate **162**



Scheme 30: Continued.

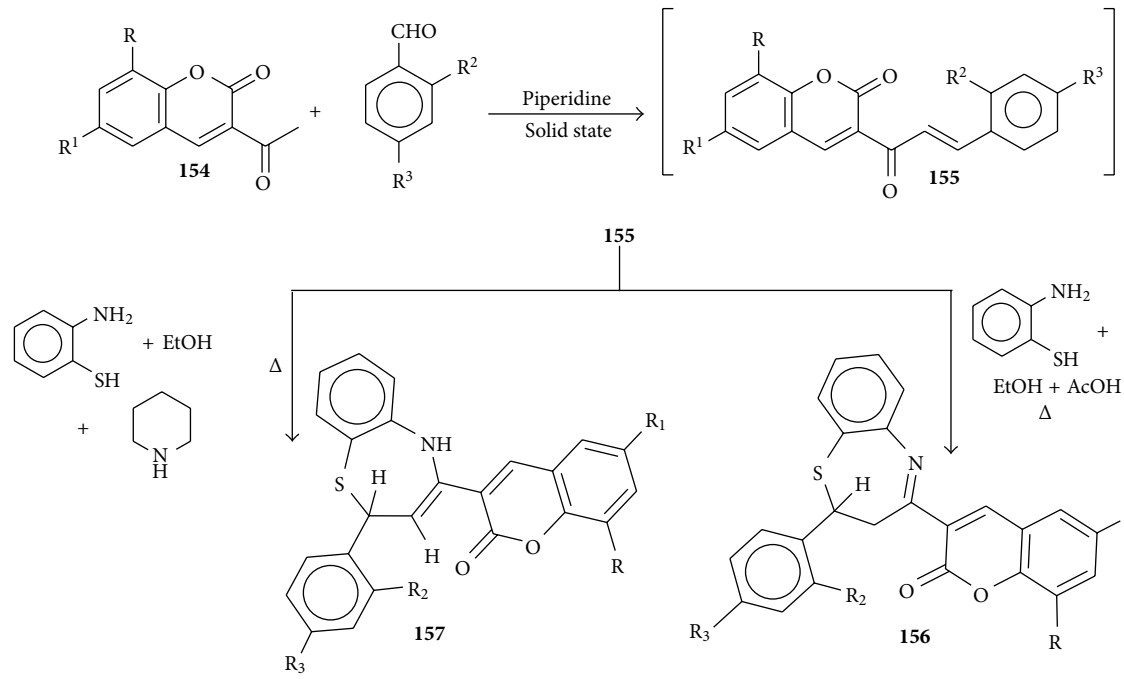


Scheme 30: Reactions of thienylidene malononitrile and *o*-aminothiophenol in the presence of catalytic amount of piperidine.

under microwave irradiation in an open vessel afforded the *trans*- and *cis*-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4-ones **163, 164**. Varying the reaction time and power output as well as the nature of the solvent controlled the disastereo-selectivity of this reaction. Carrying out the process for 20 min at a power of 390 W in toluene led to a *cis*/*trans* ratio of 9 : 1 (yield: 74%). Raising the power to 490 W for 10 min involved an inversion of the ratio, that is, increasing dramatically the amounts of the *trans*-isomer (yield: 84%). The traditional one-pot preparation of racemic target compounds **163, 164** produced less than 30% yield at 160°C with prolonged reaction times.

1,3-Dihydro-3-(2-phenyl-2-oxoethylidene)indol-2-one **165** and *o*-aminothiophenol derivatives under thermal and microwave reaction conditions using ethylene glycol afforded *spiro*[benzo[*b*][1, 4]thiazepine-2,3′-indolin]-2′-ones **166**.

To enhance the anxiolytic activity of some azepine derivatives by the introduction of a trifluoromethyl group in the dia-, oxa- or thiazepine, trifluoroacetyl ketene acetals **167** were reacted with *o*-aminothiophenol derivatives in the presence of xylene, applying a multimode microwave oven (8–12 min at 980 W). Although this methodology uses microwave inert solvents (e.g., toluene or xylene), which are not serving in the energy transfer processes, it gave the 3-substituted 2-hydroxy-2-trifluoromethyl-1,5-benzothiaz-epine derivatives **168** in good yields, suggesting absorption of the microwaves by the reactants [33, 35, 36, 39] (Scheme 33).



155	R	R^1	R^2	R^3	155	R	R^1	R^2	R^3
(a)	H	H	NO_2	H	**(f)**	H	H	H	$N(CH_3)_2$
(b)	H	H	Cl	H	**(g)**	Br	Br	Cl	H
(c)	Br	Br	NO_2	H	**(h)**	Br	Br	Cl	H
(d)	H	Br	H	$N(CH_3)_2$	**(i)**	H	H	OH	H
(e)	Br	Br	H	$N(CH_3)_2$	**(j)**	H	Br	H	H

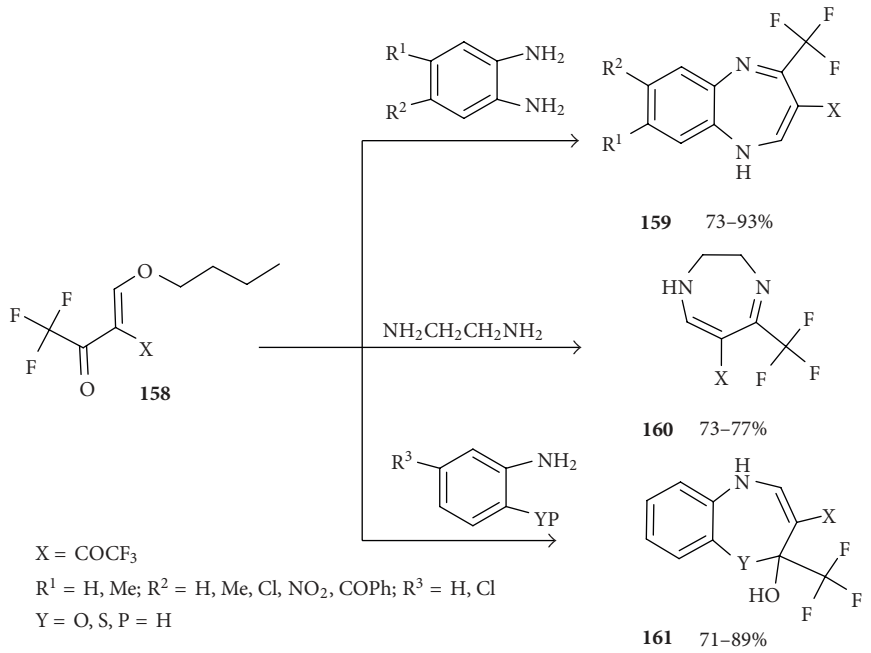
156	R	R^1	R^2	R^3	156	R	R^1	R^2	R^3
(a)	H	H	H	$N(CH_3)_2$	**(f)**	H	Br	H	$N(CH_3)_2$
(b)	H	H	Cl	H	**(g)**	H	Br	Cl	H
(c)	H	H	NO_2	H	**(h)**	Br	Br	Cl	H
(d)	Br	Br	H	$N(CH_3)_2$	**(i)**	H	Br	NO_2	H
(e)	H	H	OH	H	**(j)**	H	Br	H	H

157	R	R^1	R^2	R^3	157	R	R^1	R^2	R^3
(a)	H	H	Cl	H	**(e)**	H	Br	Cl	H
(b)	H	H	NO_2	H	**(f)**	H	H	H	$N(CH_3)_2$
(c)	H	H	OH	H	**(g)**	H	Br	H	H
(d)	H	Br	H	$N(CH_3)_2$					

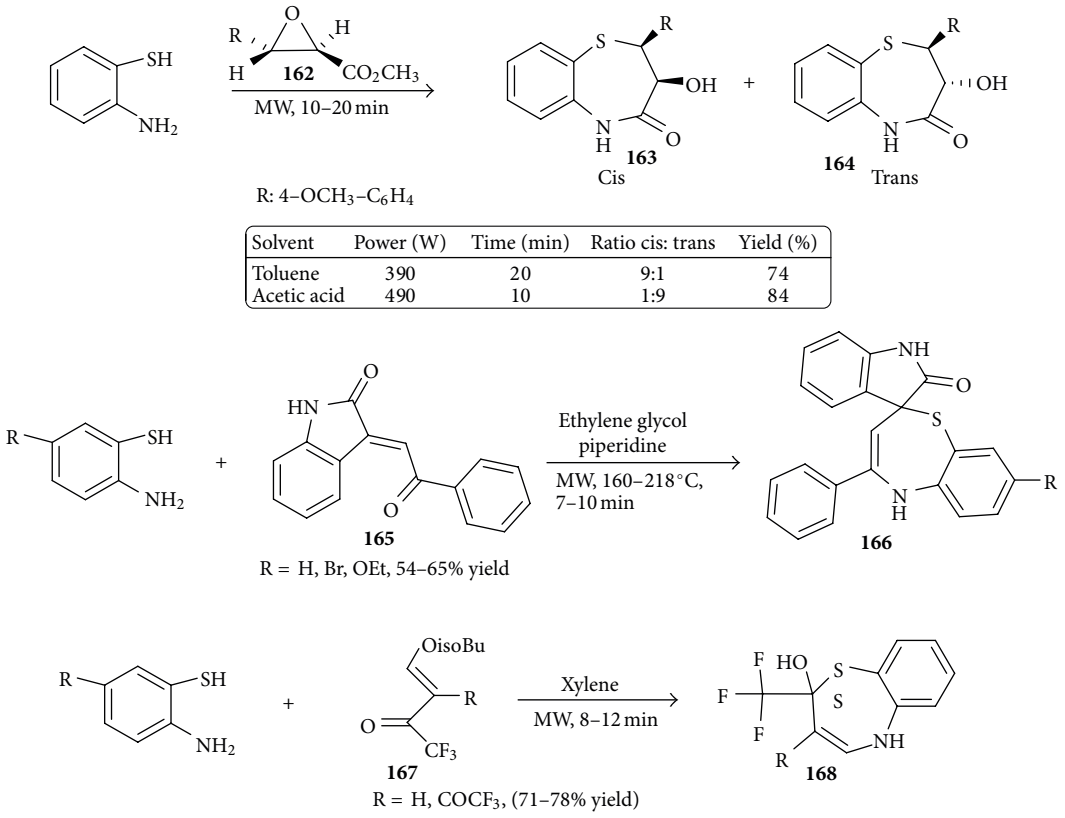
Scheme 31: Reaction of 3-[1-oxo-3-(substituted phenyl)-2-propenyl]-2*H*-1-benzopyran-2-ones with *o*-aminothiophenol in the presence of piperidine.

3.1.34. Comparative Microwave-Assisted and Conventional Heating Reactions of N-(4-(2-oxo-2H-Chromen-3-yl) thiazol-2-yl)cinnamamide with o-Aminothiophenol in the Presence of Glacial Acetic Acid as Catalyst and Methanol. *N*-[4-(2-oxo-2*H*-Chromen-3-yl)-1,3-thiazol-2-yl]acetamide **170** (prepared from3-(2-amino-1,3-thiazol-4-yl)-2*H*-chromen-2-one **169** by acetylation with acetyl chloride in chloroform) on reaction with various aldehydes **171a–j** gave *N*-(4-(2-oxo-2*H*-chromen-3-yl)thiazol-2-yl) cinnamamide derivatives **172a–j** in good yield. The latter derivatives on treatment with *o*-aminothiophenol in the presence of glacial CH_3COOH as catalyst and MeOH under MWI for afforded 2,3-dihydro-2-aryl-4-[4-(2-oxo-2*H*-chromen-3-yl)-1,3-thiazol-2-ylamino]1,5-benzothiazipine **173a–j**. Higher yields of compounds **172a–j** and **173a–j** were realized at 500 watt for 2–2.5 min of microwave irradiation, whereas similar reactions of **173a–j** under conventional heating (steam bath) at reflux gave poorer yields after much longer times [40] (Scheme 34).

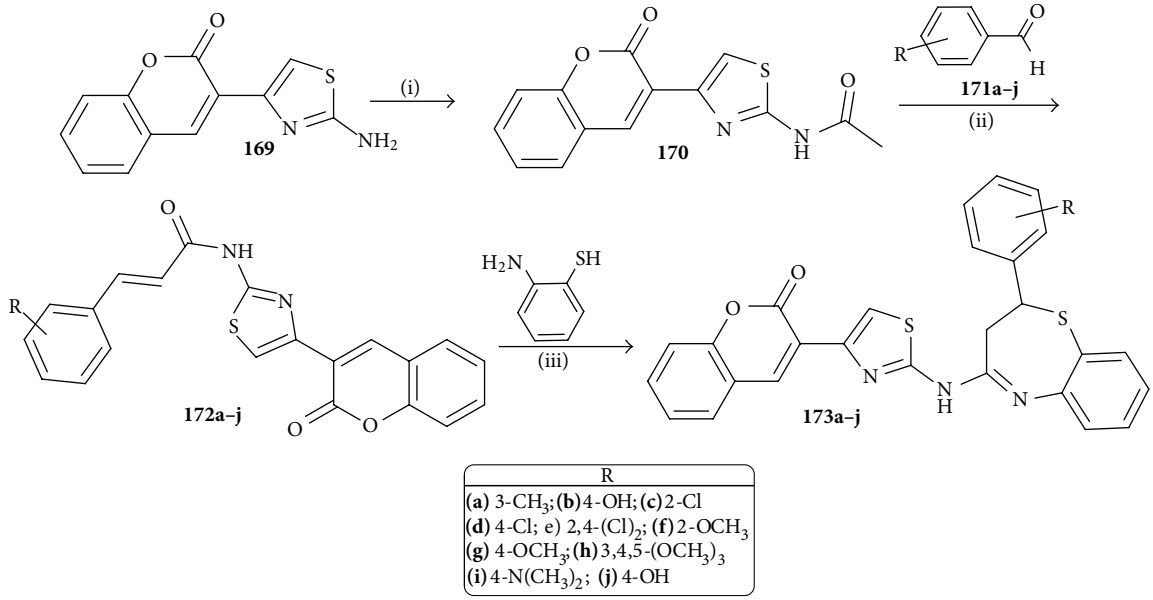
3.1.35. Reaction of 1-(4-(4,6-bis (Phenylamino)-1,3,5-triazin-2-ylamino) phenyl)-3-(4-methoxyphenyl) prop-2-en-1-ones with o-Aminothiophenol in the Presence of a Few Drops of Glacial Acetic Acid. Reaction of 2,4,6-trichloro-1,3,5-triazine with aniline in acetone at 0–5°C gave 4,6-dichloro-*N*-phenyl-1,3,5-triazin-2-amine **174**. Further reaction of **174** with aniline in acetone at room temperature yielded 6-chloro-N^2, N^4-diphenyl-1,3,5-triazine-2,4-diamine **175**. The latter product



Scheme 32: Reactions of butoxy(trifluoromethyl)enone with *o*-aminophenol or *o*-aminothiophenol derivatives.



Scheme 33: Mirowave-assisted irradiation of *o*-aminobenzenethiol and the oxirane-2-carboxylate.



Reagents and reaction conditions: (i) $CH_3COCl/CHCl_3$, 0–5° C, 8 hr. (ii) Conventional: CH_3OH/2%NaOH, reflux, 6–8 hr. microwave: CH_3OH/2%NaOH, MWI, 2–3.5 min. (iii) Conventional: CH_3OH/glacial CH_3COOH, reux, 60–70° C, 6–9 hr. Microwave: CH_3OH/glacial CH_3COOH, MWI, 2–3.5 min.

Scheme 34: Comparative microwave-assisted and conventional heating reactions of *N*-(4-(2-oxo-2*H*-chromen-3-yl) thiazol-2-yl)cinnamamide with *o*-aminothiophenol in the presence of glacial acetic acid as catalyst and methanol.

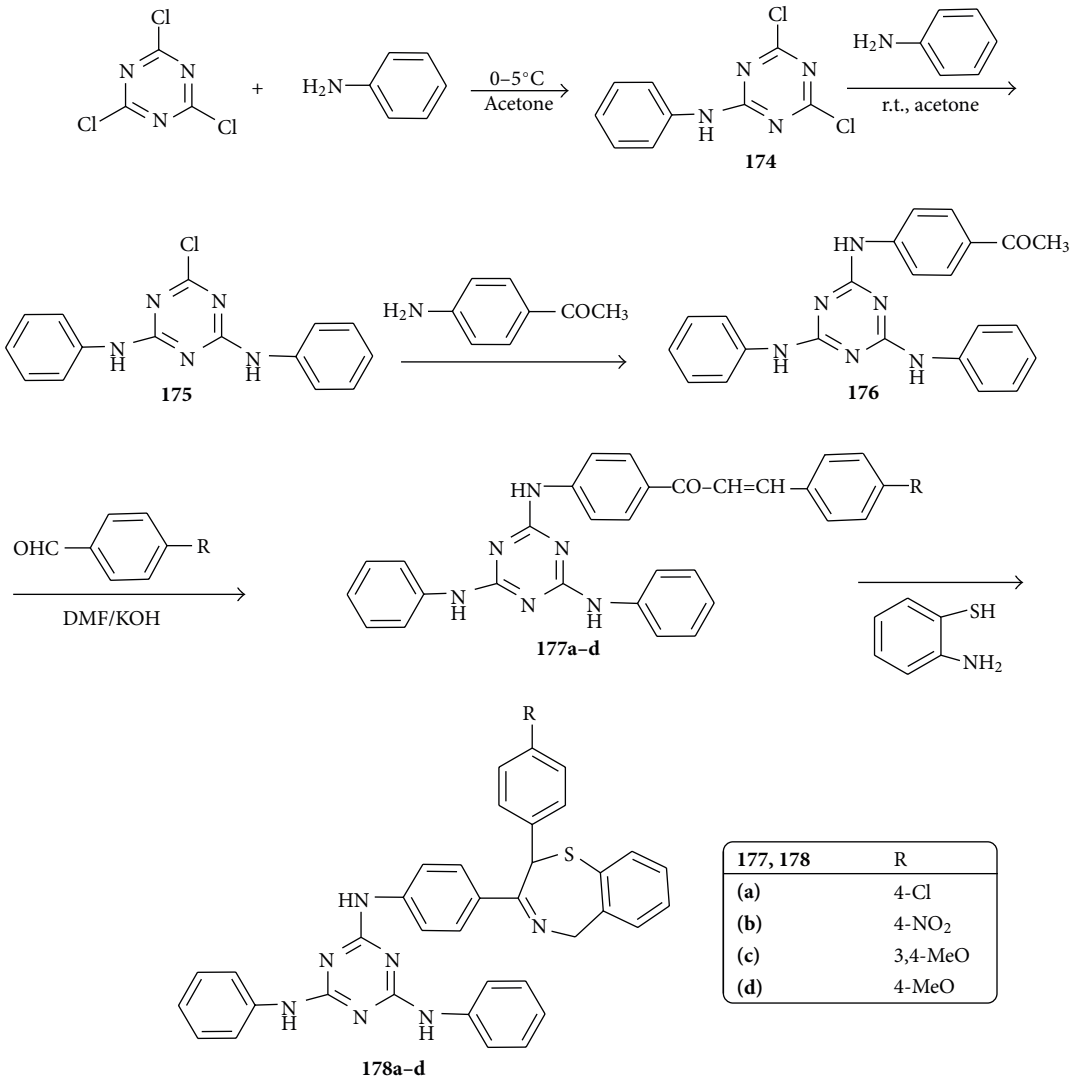
on reaction with1-(4-aminophenyl) ethanone gave 1-(4-(4,6-bis(phenylamino)-1,3,5-triazin-2-ylamino)phenyl)ethanone **176**. 1-(4-(4,6-bis(phenylami-no)-1,3,5-triazin-2-ylamino)phenyl)-3-(4-methoxyphenyl)propen1one **177d** was obtained from reaction of **176** with 4-methoxybenzaldehyde in good yield in DMF/KOH. Similarly, products **177a–d** were synthesized using the appropriate aromatic aldehydes. Reactions of **177a–d** with *o*-aminothiophenol in the presence of few drops of glacial CH_3COOH yielded 1,5-benzothiazepine **178a–d** in moderate yields (56–63%) [41–43] (Scheme 35).

3.1.36. Condensation Reactions of Enones with o-Aminothiophenol. The overall process for the formation of the hemiperfluoroenones **181** from perfluoroalkyl iodides and acylsilanes has been described previously [44, 45]. Depending on the experimental conditions, compounds **179** and **180** were isolated. The latter compounds are considered as useful synthons and regarded as equivalents of the enones **181**. Condensation of *o*-aminothiophenol, with the enones **179** (or **180** or **181**) provided the corresponding benzothiazepines **182a–c** in good yields. In the carbohydrate series, the 1,5-benzothiazepines **182c** was obtained as an epimeric mixture (*D-xylo*/*L-arabino* in a 85 : 15 ratio), indicating that a further C-4 epimerisation had occurred during the formation of the heterocycle [44–47] (Scheme 36).

3.1.37. Reaction of 1-(Benzo[d][1,3]dioxol-5-yl)-3-phenylpropane-1,3-diones with o-Aminothiophenol. 1-(Bnzo[*d*][1, 3]dioxol-5-yl)-3-phenylpropane-1,3-diones **183a–I** on reaction with *o*-aminothiophenol in pyridine under reflux for ~4 h, while stirring, afforded the 2,4-disubstituted 1,5-benzothiazepines **184a–i**. The reaction is initiated by the nucleophilic attack of sulphydryl electrons on enolic carbon atom of the β-diketone followed by loss of water molecule. Therefore, amino group comes in vicinity of carbonyl group, by dehydration resulting into the cyclized products of type **184** [48] (Scheme 37).

3.1.38. Reactions of 2-Hydroxybenzal Acetophenone and 1-(1-Naphthyl)-3-(1-naphthyl)-2-propenone with o-Aminothiophenol Derivatives. The absorbed ethanolic solutions of chalcones **187a,b** (prepared from the aldehydes **185a,b** and the ketones **186a,b** under microwave irradiation on a suitable solid support Mont. KSF) when mixed with *o*-aminothiophenol derivatives (20% by weight of the reactants) and irradiated inside a MW oven for an appropriate time at 640 W yielded the benzothiazepine **188a–g** in excellent yield.

When equimolar mixture of *o*-aminothiophenol derivatives and 2-hydroxybenzalaceto-phenone **187a** in dry ethanol was saturated with dry HCl gas until boiling and heated under reflux for 6 h the benzothiazepine products **188a–g** were synthesized (65–67% yield). Irradiation of the absorbed ethanolic solutions of **188a,b** on clay fen (prepared from 2 g clay + 0.001 mol Fe (III) NO_3) inside a microwave oven for 6 min yielded 8-ethoxy-2,5-dihydro-l,5-benzothiazepine-l,l-dioxides **189a,b** in good yields (88%) and no mono-oxide of type **190** was detected. The dioxides **189a,b** were also obtained in satisfactory yield (conventional method) *via* dissolved

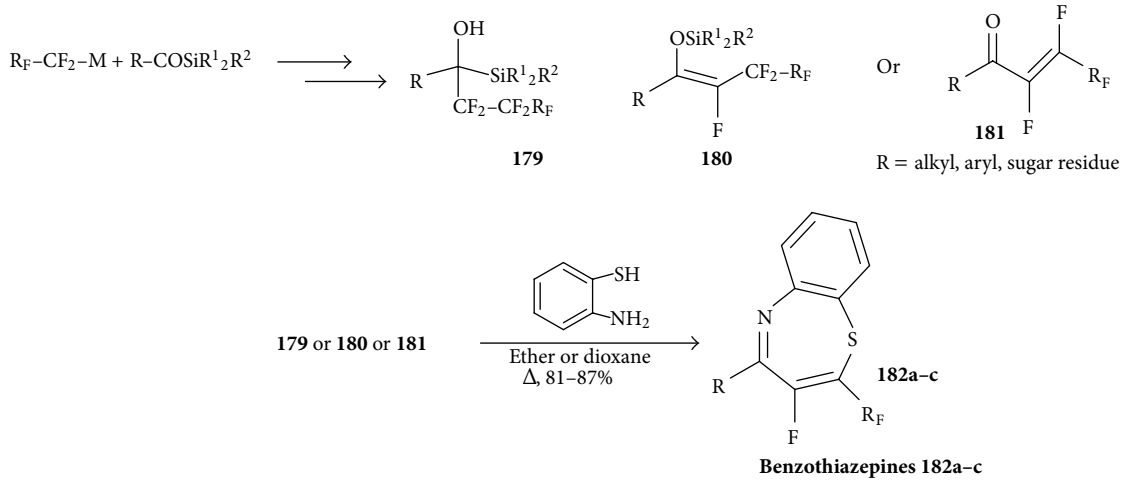


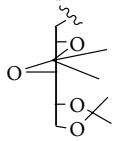
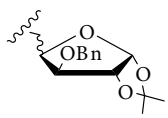
Scheme 35: Reaction of 1-(4-(4,6-bis (phenylamino)-1,3,5-triazin-2-ylamino)phenyl)-3-(4-methoxyphenyl) prop-2-en-1-ones with *o*-aminothiophenol in presence of a few drops of glacial acetic acid.

solutions of **188a,b** in glacial CH_3COOH, H_2O_2 (30%) and the mixture was boiled under reflux for 10–12 h and no traces were detected for the expected benzothiazepines of type **190** [49] (Scheme 38).

3.1.39. Reaction of (E)-N-(2-(Allylsulfonyl)phenyl)-4-methyl-N-(prop-1-enyl)benzene Sulfonamide with o-Aminothiophenol in the Presence of Grubbs' Second-Generation Catalyst. Ortho-aminothiophenol was Monoalkylated with allyl bromide and the amine subsequently protected with a tosyl group to afford *N*-(2-(allylthio)phenyl)-4-methylbenzenesulfon amide **191**. Allylation of **191** readily afforded the sulfonamide **192**. Surprisingly, ring-closing metathesis (RCM) on this substrate did not give the expected 8-membered 6-tosyl-5,6-dihydro-2*H*-benzo[*b*][1, 4]thiazocine **193** and attempted isomerization of the same substrate was also unsuccessful. Substrate **192** was thus oxidized to the corresponding sulfone **194** and the RCM successfully afforded the corresponding sulfon **195** in good yield. By applying the sequential isomerization-RCM strategy on compound **194** it was rather surprising to isolate *N*-(2-(allylsulfonyl)phenyl)-4-methyl-*N*-(prop-1-enyl) benzenesulfonamide **196** in which only the *N*-allyl group had been isomerized. Subsequently, when compound **196** was treated with Grubbs'second-generation catalyst **197**, the 7-membered 2,5-dihydro-1,5-benzothiazepine1,1-dioxide **198** was obtained in fair yield; although the reaction was particularly slow [50] (Scheme 39).

3.1.40. Reaction of Substituted Chalcones with o-Aminothiophenol: Formation of Benzothiazepines Depended on Chalcone Substituents. Reaction of chalcones **199** with *o*-aminothiophenol in the presence of silica-gel that was carried out under solvent-free conditions afforded 2,3-dihydro-2,4-diphenyl-1,5-benzothiazepine **200** in one step in good yield. This reaction depended on the chalcone substituents. In the case of chalcones having NO_2 and OH groups,

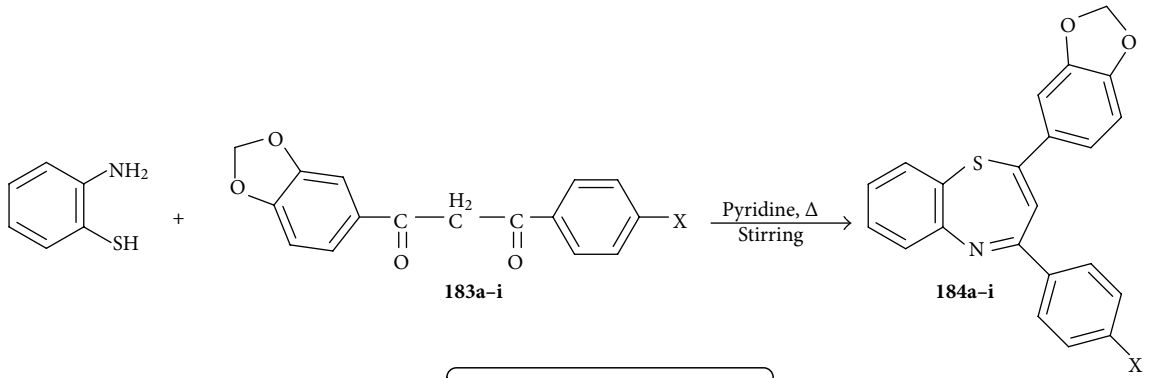


Compound	R	R^1	R^2	R_F	Yield (%)
181 (a)	Ph	Me	Me	C_4F_9	88
(b)	*p*-Cl-Ph	Me	Me	C_4F_9	91
(c)	*p*-F-Ph	Me	Me	C_4F_9	89
(d)	*p*-MeO-Ph	Me	Me	C_4F_9	87
(f)		Me	Me	C_2F_5	88
(g)		Me	Me	C_2F_5	67

Starting compound	R_F	Yield (%)
181 (c)	C_4F_9	**182 (a)** 87
(f)	C_2F_5	**(b)** 81
(g)	C_2F_5	**(c)** 79[(a)]

[(a)] Mixture of the two epimers (D-d-xylo/ L-arabino, 85:15

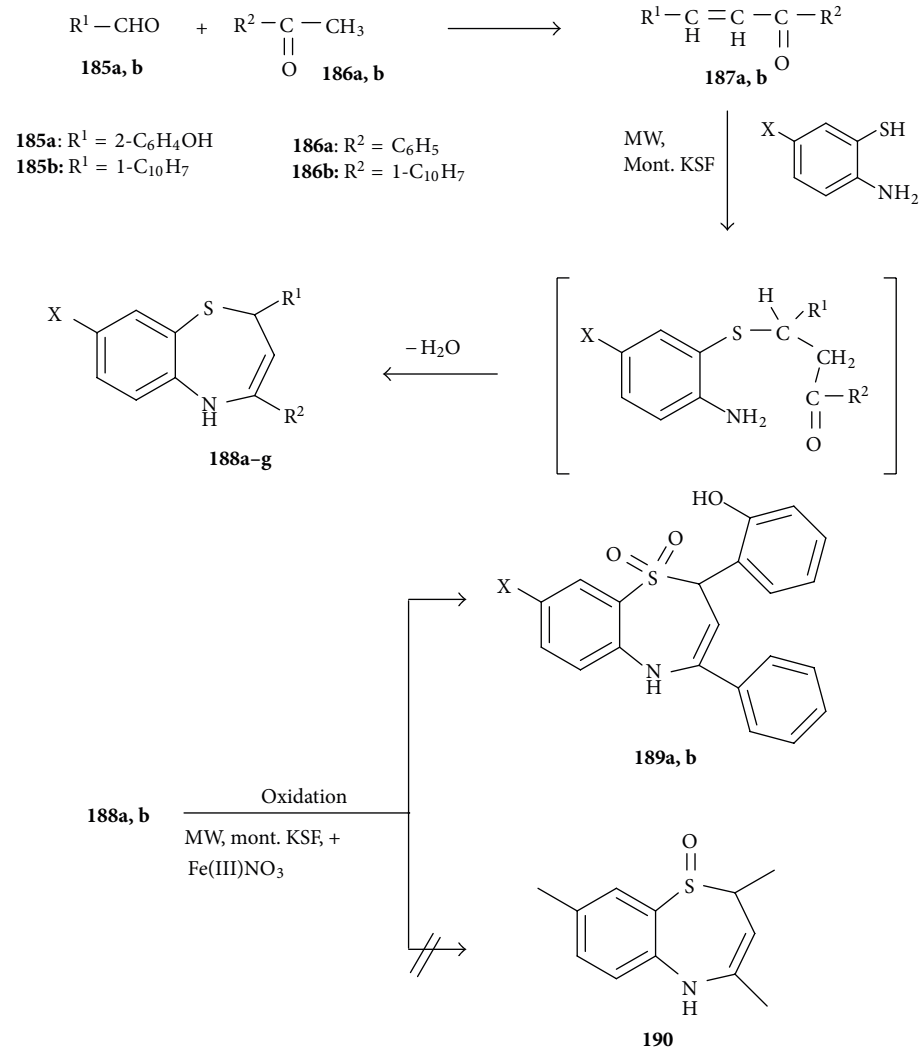
Scheme 36: Condensation reactions of enones with *o*-aminothiophenol.



183,184	X	183,184	X
(a)	H	**(f)**	OH
(b)	CH_3	**(g)**	NH_2
(c)	Cl	**(h)**	NO_2
(d)	Br	**(i)**	OC_2H_5
(e)	OCH_3		

Scheme 37: Reaction of 1-(benzo[*d*][1, 3]dioxol-5-yl)-3-phenylpropane-1,3-diones with *o*-amino thiophenol.

the yields were lower (44–68%) than those of chalcones with the other substituents. It seems that low reactivity of chalcones having NO_2 and OH groups is due to these groups being absorbed more strongly on the surface of silica-gel than that of a carbonyl group in the same molecule. Meanwhile, chalcones **199** when reacted with *o*-aminothiophenol in refluxing toluene, the chalcones with electron-donating substituents such as CH_3 and OCH_3 group, gave only *β*-phenyl-*β*-(2-aminophenylmercapto)-propiophenones of type **199A**, whereas from chalcones with



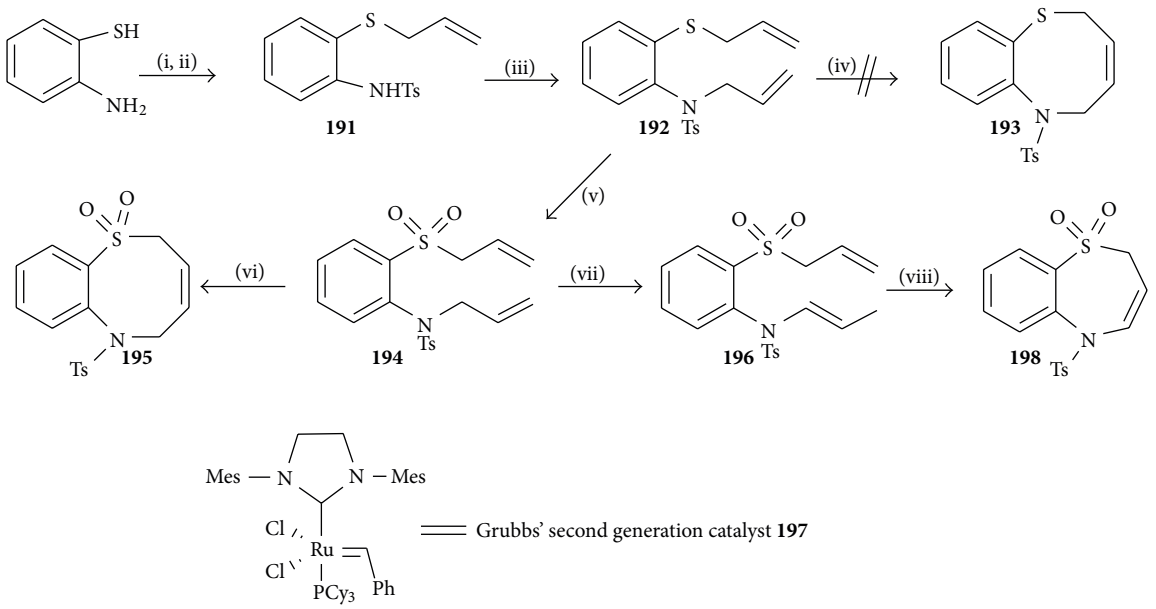
Compd	X	R^1	R^2	Compd	X	R^1	R^2
188a	OC_2H_5	2-C_6H_4OH	C_6H_5	**188f**	OCH_3	1-$C_{10}H_7$	1-$C_{10}H_7$
b	CH_3	2-C_6H_4OH	C_6H_5	**g**	CH_3	1-$C_{10}H_7$	1-$C_{10}H_7$
c	OCH_3	2-C_6H_4OH	C_6H_5	**189a**	OC_2H_5	2-C_6H_4OH	C_6H_5
d	Cl	2-C_6H_4OH	C_6H_5	**b**	CH_3	2-C_6H_4OH	C_6H_5
e	Br	2-C_6H_4OH	C_6H_5				

Scheme 38: Reactions of 2-hydroxybenzal acetophenone and 1-(1-naphthyl)-3-(1-naphthyl)-2-propenone with *o*-aminothiophenol derivatives.

electron-withdrawing substituents such as NO_2 group, only 1,5-benzothiazepines were formed. Therefore, the carbonyl group in chalcones having NO_2 or OH groups is less activated than that in chalcones with the other substituents [51, 52] (Scheme 40).

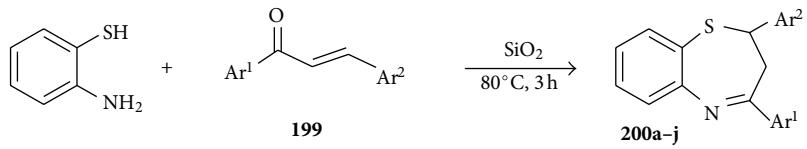
3.1.41. Synthesis of Fluorinated Azeto[2,1-d][1,5]benzothiazepine from 2-Carboxy-2,3-dihydro-1,5-benzothiazepine Using Conventional and Microwave-Assisted Reactions. A mixture of substituted *ortho*-aminothiophenol derivatives, 3-(substituted benzoyl)-2-propionic acid **201** and montmorillonite KSF was dissolved in acetone, swirled for a while and excess solvent was removed under gentle vacuum. The obtained dry flowing powder was irradiated under microwave oven for short time. After completion of the reaction (monitored by TLC) and filtration of the recyclable inorganic solid support, the 2-carboxy-2,3-dihydro-1,5-benzothiazepines **202a–m** were obtained in good yield [53] (Scheme 41).

3.1.42. Reactions of o-Aminothiophenol Derivatives with Isatin and 3-Methyl-1-phenyl-2-pyrazolin-5-one under MW Irradiation in the Presence of Montmorillonite KSF. A neat mixture of isatin **203** and 3-methyl-1-phenyl-2-pyrazolin-5-one **204** placed on an alumina bath and irradiated



Reagents and conditions: (i) allyl bromide, MeOH, NaOH, H_2O, rt, 2 h; (71%); (ii) TsCl, pyridine, CH_2Cl_2, 45°C, N_2, 24 h (97%); (iii) K_2CO_3, allyl bromide, acetone, rt, 24 h; (99%); (iv) 5% catalyst 7,toluene, 50°C, N_2, 48 h, complex mixture; (v) MCPBA (2.2 equiv), CH_2Cl_2, −5°C, 48 h; (71%); (vi) 5% catalyst 197, $CHCl_3$, rt, 24 h, then 45°C, 24 h (95%); (vii) 10% $[RuClH(CO)(PPh_3)_3]$, toluene, 105°C, 24 h(84%); (viii) 5% catalyst **197**, toluene, 50°C, 24 h, then further 5% catalyst **197** 80°C, 24 h, **198** (41%) and **196** (59%).

Scheme 39: Reaction of (*E*)-*N*-(2-(allylsulfonyl)phenyl)-4-methyl-*N*-(prop-1-enyl)benzenesulfonamide with *o*-aminothiophenol in the presence of Grubbs' second-generation catalyst.



Synthesis of 1,5-benzothiazepines **200a–j**[a]

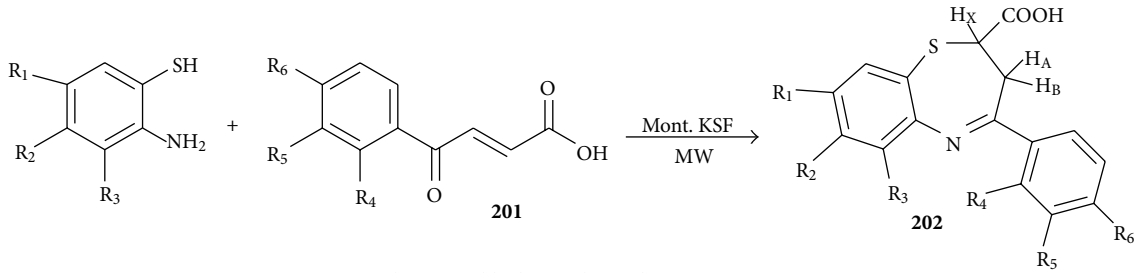
199 or **200**	Ar^1	Ar^2	Yield (%) of **3**	**199** or **200**	Ar^1	Ar^2	Yield (%) of **3**[b]
(a)	C_6H_5	C_6H_5	87	**(f)**	C_6H_5	4-ClC_6H_4	78
(b)	4-ClC_6H_4	C_6H_5	75	**(g)**	C_6H_5	4-$CH_3OC_6H_4$	83
(c)	4-$CH_3C_6H_4$	C_6H_5	73	**(h)**	C_6H_5	4-$CH_3OC_6H_4$	74
(d)	4-$CH_3OC_6H_4$	C_6H_5	61	**(i)**	C_6H_5	4-HOC_6H_4	44
(e)	4-$CH_3OC_6H_4$	C_6H_5	44	**(j)**	C_6H_5	4-$NO_2C_6H_4$	68

[a] Mol ratio 1:2 = 1.5, 80 °C, 3h, (2g); [b] Isolated yield.

Scheme 40: Reaction of substituted chalcones with *o*-aminothiophenol: formation of benzothiazepines depended on chalcone substituents.

for 6–8 minutes gave 3-(3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4(5*H*)-ylidene)indolin-2-one **205** in quantitative yield. Conventional synthesis *via* heating **203** and **204** in EtOH afforded *spiro*[dipyrazolopyran3*H*-indol]-2*H*-one **206** as major product along with the indilone **205** and required a tedious work during isolation. Reactions of the intermediate **205** synthesized *"in situ"* with *o*-aminothiophenol derivatives were examined under MW irradiation using different solid supports including acidic, basic, or neutral alumina, silica, montmorillonite KSF, and K10. The montmorillonite K10 was found the most adaptable and simplest catalyst for synthesizing *spiro*[indole-pyrazolo[4, 3-c][1, 5]benzothiazepines **207a–e**, since comparatively a higher yield (72–91%) was achieved in shorter reaction time (~7 min.) by this method.

The best results obtained under microwave irradiation were extrapolated to conventional heating. Thus, in the case of compound **207a** when the reaction was carried out using a preheated oil-bath under the same reaction conditions (time, temperature, pressure, and vessel) it did not occur and the reactants remained unchanged even on extended reaction times, suggesting that the effect of



2-carboxy-2,3-dihydro-1,5-benzothiazepines (**202a–m**)

202	R_1	R_2	R_3	R_4	R_5	R_6	Time (min)	Yield (%)
(a)	CH_3	H	H	H	H	F	4	80
(b)	F	H	H	H	H	F	3	82
(c)	Cl	H	H	H	H	F	4	75
(d)	Br	H	H	H	H	F	5	81
(e)	OCH_3	H	H	H	H	F	4	70
(f)	OC_2H_5	H	H	CH_3	H	F	4	73
(g)	C_2H_5	H	H	CH_3	H	F	3	78
(h)	H	CF_3	H	H	Cl	H	5	80
(i)	H	H	Br	H	CF_3	H	4	76
(j)	CF_3	H	H	H	H	OH	6	75
(k)	H	H	Cl	H	H	F	5	78
(l)	H	H	CF_3	CH_3	H	F	3	82
(m)	H	CH_3	CH_3	H	CF_3	H	6	74

Scheme 41: Synthesis of fluorinated azeto[2,1-*d*][1, 5]benzothiazepine from 2-carboxy-2,3-dihydro-1,5-benzothiazepine using conventional and microwave-assisted reactions.

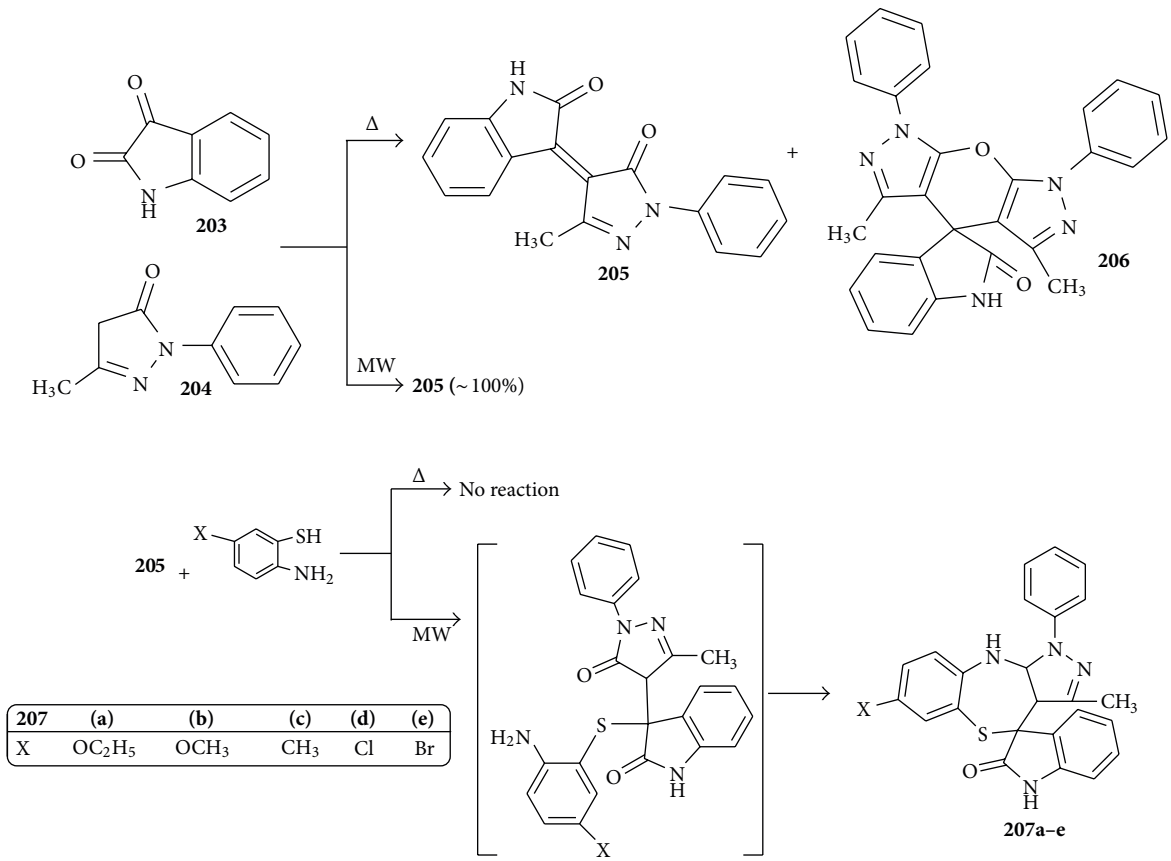
microwave irradiation is not simply thermal process [54] (Scheme 42).

3.1.43. Microwave Thermal Reaction of Alkynone with o-Aminothiophenol. As a model reaction, *p*-chlorobenzoyl chloride **208b** and phenyl acetylene **209a** were first reacted under Sonogashira conditions for 1 h at room temperature to furnish the expected alkynone, and after the subsequent addition of *o*-aminothiophenol and acetic acid (upon varying reaction temperature under microwave irradiation and time) led to the formation of benzothiazepine **210b**. This optimization of hetero-cyclisation clearly showed that dielectric heating is superior over conductive heating.

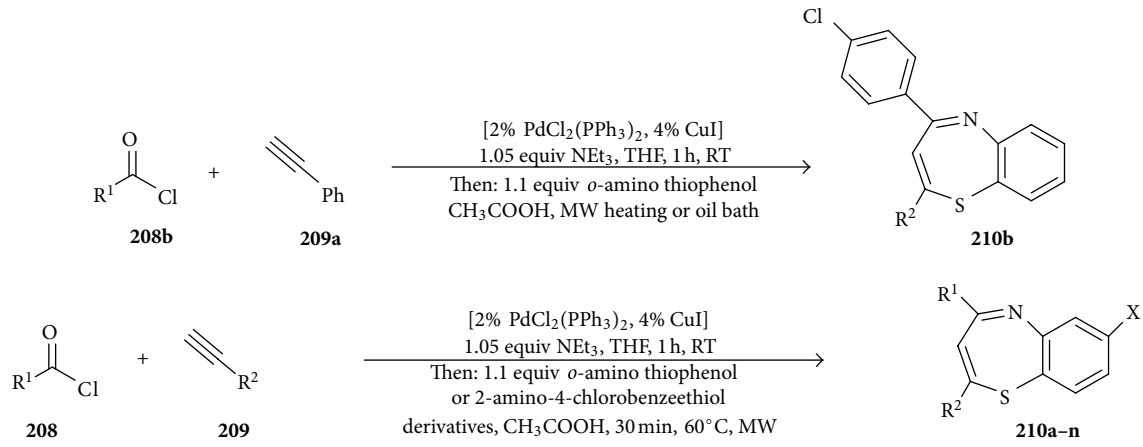
In comparison to the other known MCR synthesis of benzo[*b*][1, 5]diazepines this result is just converse. Although the Michael addition and cyclo-condensation were essentially completed after 10 min at 60°C in the microwave cavity for electronically diverse substitution and a reaction time of 30 min at 60°C was chosen as the optimal condition.

With these optimizations in hand, a series of acid chlorides **208**, alkynes **209**, and the *o*-aminothiophenol or 2-amino-4-chlorobenzenethiol derivatives were submitted to the coupling-addition/cyclo-condensation sequence to give various 2,4-disubstituted benzo[*b*][1, 5]thiazepines **210a–n** as yellow to brown or red solids or resins in fair to good yields [55] (Scheme 43).

3.1.44. Comparative Microwave-Assisted and Conventional Thermal Reactions of trans-5-Methyl-3-[p-(3′-aryl-acryl-1′-oyl)-phenyl]-3H-2-oxo-Δ^4-1,3,4-oxadiazoles with o-Aminothiophenol. 4-Acetylphenylsydnone **211** (conveniently prepared from *p*-aminoacetophenone) when reacted with an aromatic aldehyde **212a–d** in EtOH afforded *trans*-3-[*p*-(3′-aryl acryl-1′-oyl) phenylsydnone **213a–d** as predominant products (*Claisen-Schmidt reaction*). The *trans* isomer are favored, since in the transition state, two large substituents are not eclipsed and there is no interference with co-planarity of the enolate system. The *trans* **213a–d** on bromination in Ac_2O sydnone ring underwent 1,3-dipolar cycloaddition to give *meso*-3-[*p*-(2′,3′-dibromo-3′-aryl-propion-1′-yl)-phenyl]-5-methyl-3*H*-2-oxo-Δ^4-1,3,4-oxadiazole **214a–d**. During cycloaddition reaction, chalcone moiety was also brominated. The dibromo derivative **214a–d** on treatment with *o*-aminothiophenol did not form the target benzothiazepines **218a–d**. Therefore, this method was not advantageous due to the bromination of chalcone moiety. Upon changing the strategy, product **211** was brominated in presence of CH_3COOH to 4-bromo-3-(4′-acetyl)-phenylsydnone **215**, which upon treatment with aromatic aldehydes **212a–d** in EtOH afforded *trans*-4-bromo-3-[*p*-(3′-aryl- acryl-1′-oyl)] phenylsydnone **216a–d**. The latter compounds upon heating in the presence of Ac_2O at 135°C or under microwave irradiation syndone ring underwent 1,3-dipolar cycloaddition along with the elimination of bromine as acetyl bromide to afford exclusively *trans* 5-methyl-3-[*p*-(3′-aryl-acryl-1′-oyl)-phenyl]-3*H*-2-oxo-Δ^4-1,3,4-oxadiazoles **217a–d**. Nucleophilic addition of sulfhydryl electrons of *o*-aminothiophenol on $C_{2'}$ of **217a–d,** is followed by intermolecular dehydrative cyclisation to afford the final benzothiazepine products **218a–d** (MW: 84–90% yield, time 8–11 min.; thermal: 49–62% yield, time: 175–190 min.). Upon comparing the synthesis by microwave assisted method with the conventional method, it was observed that the reaction progressed very fast with excellent yield in the

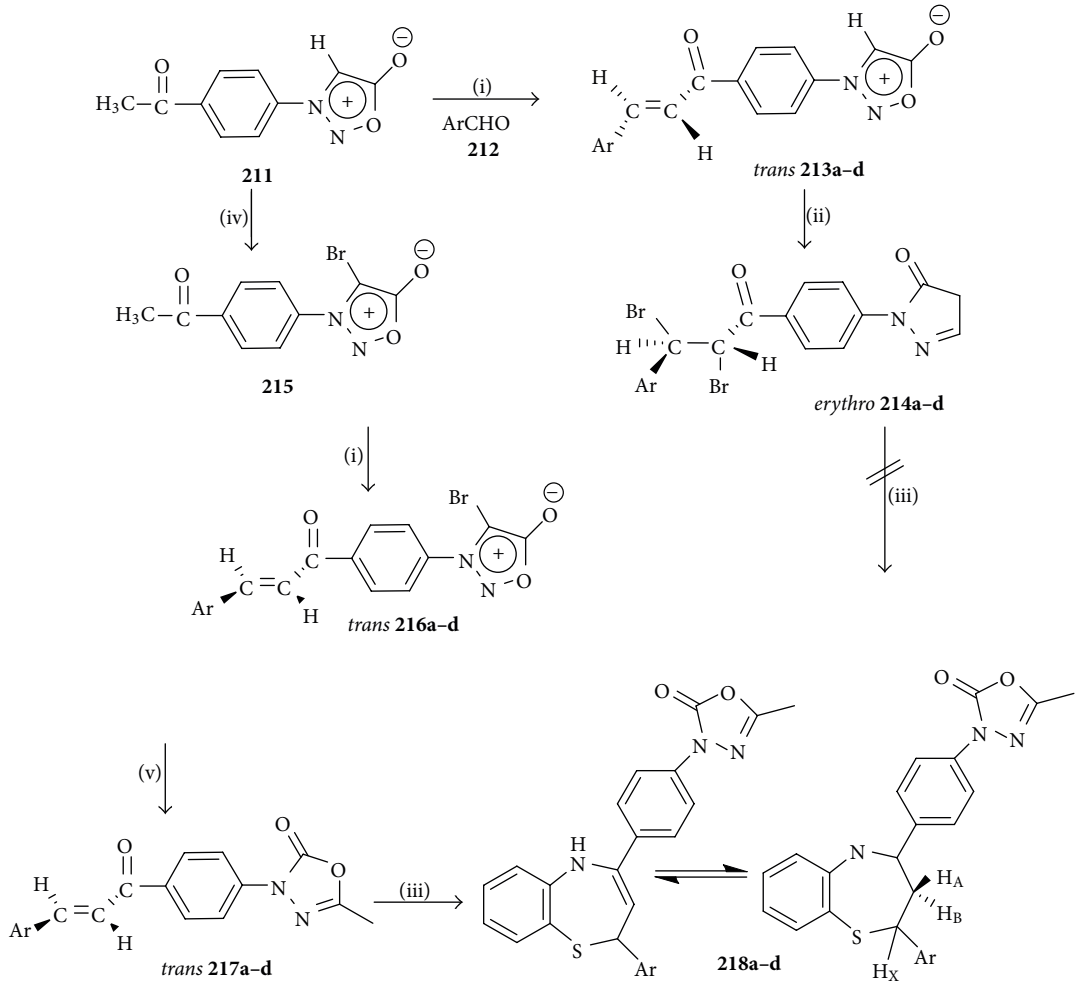


Scheme 42: Reactions of *o*-aminothiophenol derivatives with isatin and 3-methyl-1-phenyl-2-pyrazolin-5-one under MW irradiation in presence of montmorillonite KSF.



210	R^1	R^2	X	Yield (%)	210	R^1	R^2	X	Yield (%)
(a)	4-CN-C_6H_4	C_6H_5	H	68	**(h)**	4-Cl-C_6H_5	3-pyridyl	H	57
(b)	4-Cl-C_6H_4	C_6H_5	H	73	**(i)**	4-OMe-C_6H_5	4-F-C_6H_4	H	68
(c)	4-OMe-C_6H_4	C_6H_5	H	65	**(j)**	4-Cl-C_6H_5	ferrocenyl	H	57
(d)	3-Me-C6H_4	4-OMe-C_6H_4	H	77	**(k)**	4-OMe-C_6H_5	4-CN-C_6H_4	H	59
(e)	2-furyl	C_6H_5	H	60	**(l)**	4-OMe-C_6H_4	$SiMe_3$	Cl	48
(f)	2-thienyl	$SiMe_3$	H	45	**(m)**	2-Thienyl	C_6H_5	Cl	61
(g)	4-Cl-C_6H_4	C_6H_5	H	65	**(n)**	4-Cl-C_6H_5	C_6H_5	Cl	61

Scheme 43: Microwave thermal reaction of alkynone with *o*-aminothiophenol.



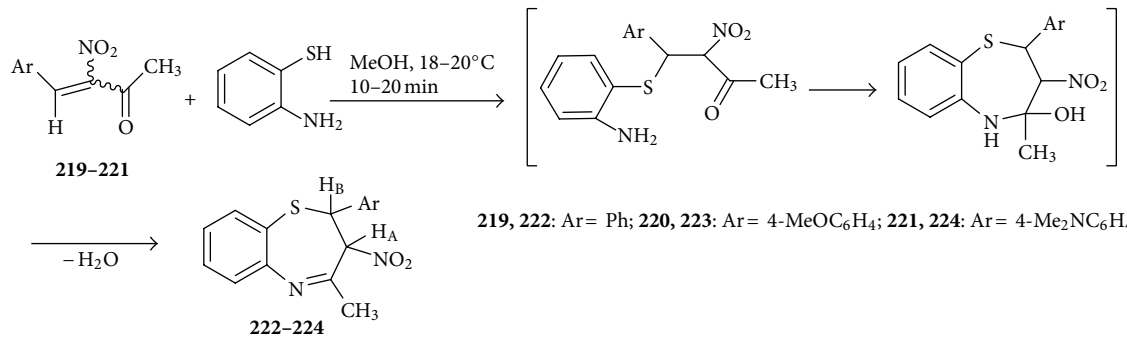
(a) Ar = Ph, (b) Ar = *p*-BrC_6H_4-, (c) Ar = *p*-$CH_3C_6H_4$, (d) Ar = *p*-ClC_6H_4
(i) ArCHO (**212a–d**), NaOH/ethanol, (ii) Br_2 in Ac_2O, (iii) o-amino thiophenol, ethanol/H^+
(iv) Br_2 in AcOH (v) Ac_2O

Scheme 44: Comparative microwave-assisted and conventional thermal reactions of *trans* 5-methyl-3-[*p*-(3′-aryl-acryl-1′-oyl)-phenyl]-3*H*-2-oxo-Δ^4-1,3,4-oxadiazoles with *o*-amino thiophenol.

former. Microwave irradiation facilitates polarization of the molecule under irradiation causing rapid reaction to occur. This is consistent with the reaction mechanism, which involves a polar transition state [56] (Scheme 44).

3.1.45. Noncatalytic Reaction of Nitro Enones with o-Aminobenzenethiol. Reactions of nitro enones **219–221** with *o*-aminobenzenethiol occurred very readily at 18–20°C in methanol (without a catalyst) and completed in 10–20 min. Crystalline 2-aryl-4-methyl-3-nitro-2,3-dihydro-1,5-benzothiazepines **222–224** separated in excellent yields (98–81%) and diastereoisomerically pure. Presumably, the process of this reaction follows nucleophilic addition pattern with subsequent heterocyclization of *S*-adducts [57] (Scheme 45).

3.1.46. Reaction of 2-(Bromomethyl)-1-sulfonylaziridines with 2-Aminothiophenol in THF in the Presence of K_2CO_3: A Regio- and Stereocontrolled Synthesis of trans-2-Phenyl- and trans-4-(phenyl or propyl)-3-sulfonamido-2,3,4,5-tetrahydro-1,5-benzothiazepines. 2-(Bromomethyl)aziridines **226a–c** were prepared from ally sulfonamides **225**. Aziridination of allylic alcohols **227** afforded the corresponding 2-(hydroxymethyl)-1-tosylaziridines and subsequently sulfonylated to 2-(sulfonyloxymethyl) aziridines **228a–c**. Treatment of 2-(bromomethyl) aziridines **226** with 1.2 equiv of *o*-aminothiophenol provided 3-sulfonamido-2,3,4,5-tetrahydro-1,5-benzothiazepines **230** in good yield. The presence of the corresponding acyclic intermediates **229** could be confirmed by means of ^{1}H NMR spectroscopy, implying that the formation of benzothiazepines **230** proceeds through initial attack of the sulfur atom of



Scheme 45: Noncatalytic reaction of nitro enones with *o*-aminobenzenethiol.

o-aminothiophenol onto the less hindered aziridine carbon atom, followed by nucleophilic displacement of bromide by the amino group. This approach was further elaborated towards *trans*-disubstituted 2,3,4,5-tetrahydro-1,5-benzothiazepines **231** and **232** starting from *trans*-2,3-disubstituted aziridines **228**. Surprisingly, treatment of 2-(sulfonyloxymethyl)aziridines **228a**,**b** with 1 : 1 equiv of *o*-aminothiophenol in THF in the presence of 1 : 1 equiv of K_2CO_3 afforded 4-substituted 3-aminobenzothiazepines **231a,b** in fair yields; whereas aziridine **228c** was transformed into 2-phenyl-3-aminobenzothiazepine **232** by applying the same reaction conditions. In both cases, no traces of the other region isomers were identified in the reaction mixtures. Apparently, tosylates **228a,b** are more reactive as compared to mesylate **228c**. Indeed, 2-(tosyloxymethyl) aziridines **228a,b** undergo initial nucleophilic displacement of the tosyloxy group by means of *o*-aminothiophenol towards intermediate aziridines **233**, which cyclizes spontaneously to afford 4-substituted 3-aminobenzothiazepines **231** (pathway a). On the other hand, 2-(mesyloxymethyl) aziridine **228c** suffers from initial ring opening by 2-aminothiophenol at the benzylic position towards acyclic intermediate **234**, followed by cyclization upon nucleophilic substitution of the mesyloxy moiety (pathway b) [58] (Scheme 46).

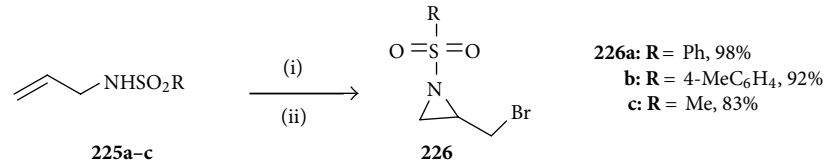
3.1.47. Intramolecular Cyclization through Dehydration of Ethyl 2-(2-Aminophenylthio)-4-oxo-4-p-substitutes-phenyl-butanoate via Heating. 2-Enoic acids **235a–f** were prepared by treating different substituted benzene with commercially available maleic anhydride in the presence of anhydrous $AlCl_3$. When these acids reacted with C_2H_5OH, then conjugate addition with *o*-aminothiophenol leads to ethyl 2-(2-aminophenylthio)-4-oxo-4-*p*-substitutes-phenyl-butanoate **237a–f** passing with the enoates **236a–f**. On heating in ethanol, **237a–f** underwent intramolecular cyclization through dehydration to afford the thiazepines **238a–f** (yield unreported) [59] (Scheme 47).

3.1.48. Reactions of 3-(2-Chlorophenyl)-1-(4-chlorophenyl)-2-propenone and 3-(2-Chlorophenyl)-1-(2-thienyl)-2-propenone with 5-Substituted-2-aminobenzenethiols in the Presence of Dry HCl Gas and in Dry Ethanol. When equimolar quantities of 3-(2-chlorophenyl)-1-(4-chlorophenyl)-2-propen-one **240a,** 3-(2-chlorophenyl)-1-(2-thienyl)-2-propenone **240b** (prepared from reactions of *o*-chlorobenzaldehyde and the proper ketones **239a** or **b**) reacted with 5-substituted-2-aminobenzenethiol derivatives in the presence of dry HCl gas and in dry EtOH the 2-(2-chlorophenyl)-4-(4-chlorophenyl/2-thienyl)-2,5-dihydro-8-substituted-1,5-benzothiaze-pines **241a–l** were afforded in 68–58% yield.

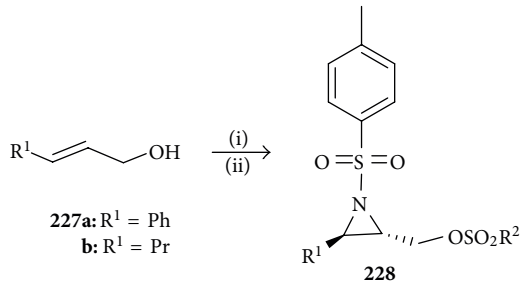
It was established that such reactions take place in two steps. In the first step, nucleophilic attack by the sulfhydryl electrons of 5-substituted-2-aminobenzenethiols takes place on the activated β-carbon atom of the α,β-unsaturated carbonyl compounds to give Michael-adduct type intermediates, which simultaneously undergo dehydrative cyclization to give final products in the second step. The formation of the intermediate and/or cyclized product was found to depend significantly on the reaction conditions. Also, the cyclized products were obtained in a single step in maximum yields in an acidic medium, that is, in methanol/ethanol saturated with dry hydrogen chloride gas [60] (Scheme 48).

3.1.49. Reactions of 6-Arylidene-2,3-dimethyl/3-methyl-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-ones with 2-Aminothiophenol in Dry (EtOH/HCl Gas). 6-Arylidene-2,3-dimethyl/3-methyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one **243a** was obtained by the condensation of 2,3-dimethylbenzocyclohepten-5-one **242a** with appropriate aldehyde. Compound **243a** reacted with *o*-aminothiophenol in dry ethanol and dry HCl gas (passed with the reaction mixture until its saturation). The usual workup gave 2,3-dimethyl-8-phenyl-6,7,7a,8-tetrahydro-5*H*-9-thia-14-azadibenzo[*a*,*i*]he-ptalene **244a** (in 63% yield) along with a small amount of a dimer **245** as a side product. Under analogous conditions, the reaction of 6-arylidene-2,3-dimethyl/3-methyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one **243b–l** with 2-aminothiophenol in ethyl alcohol afforded 1,5-benzothiazepine derivatives **244b–l**, respectively (55–65% yield) [61–63] (Scheme 49).

3.1.50. Thermal Condensation of o-Aminobenzenethiol Derivatives with Methyl trans(±)-3-(4-methoxyphenyl)glycidate in Xylene. Synthesis of (±)*cis*-2-(4-methoxyphenyl)-3-hydroxy-2,3-dihydro-1,5-benzothia-zepin-4(5H)-ones **247**

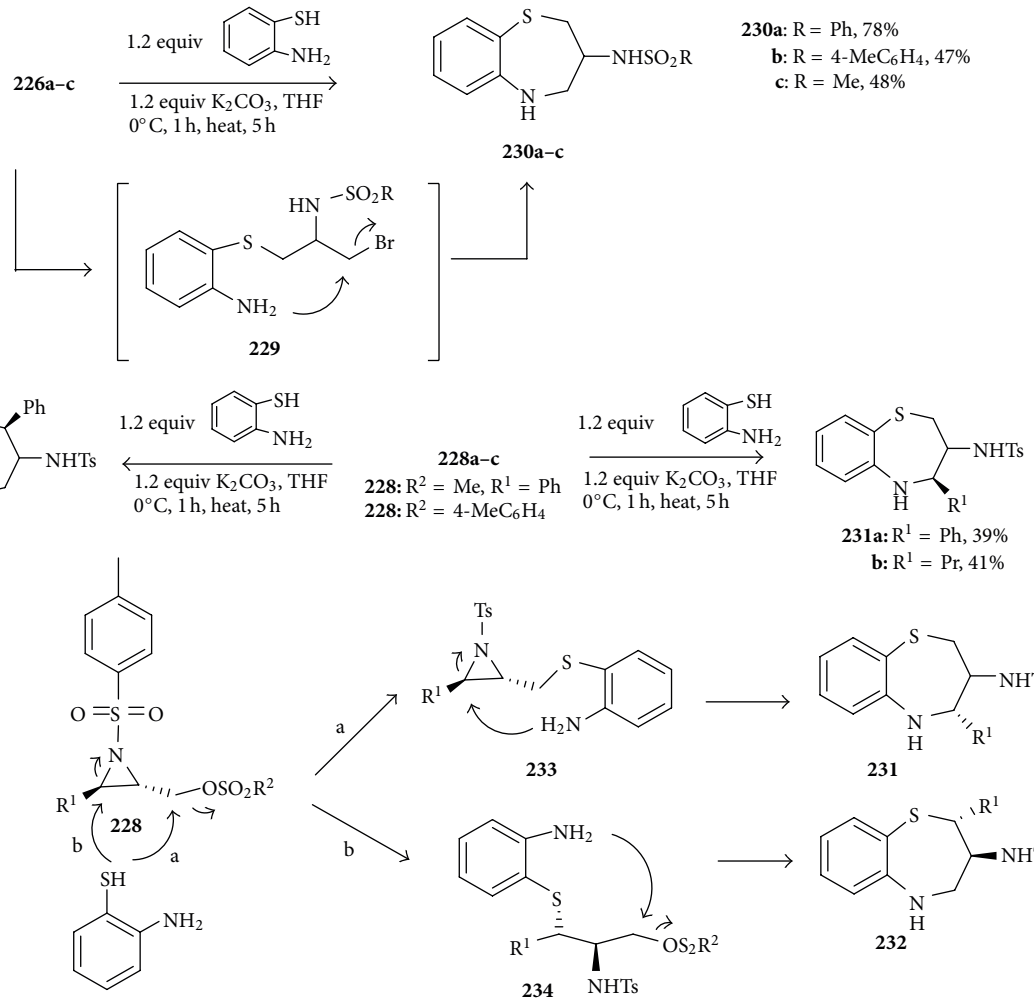


(i) 1 equiv Br_2, CH_2Cl_2, 0, r.t., 1 h; (ii) 1N NaOH, r.t., 0.3–15 h

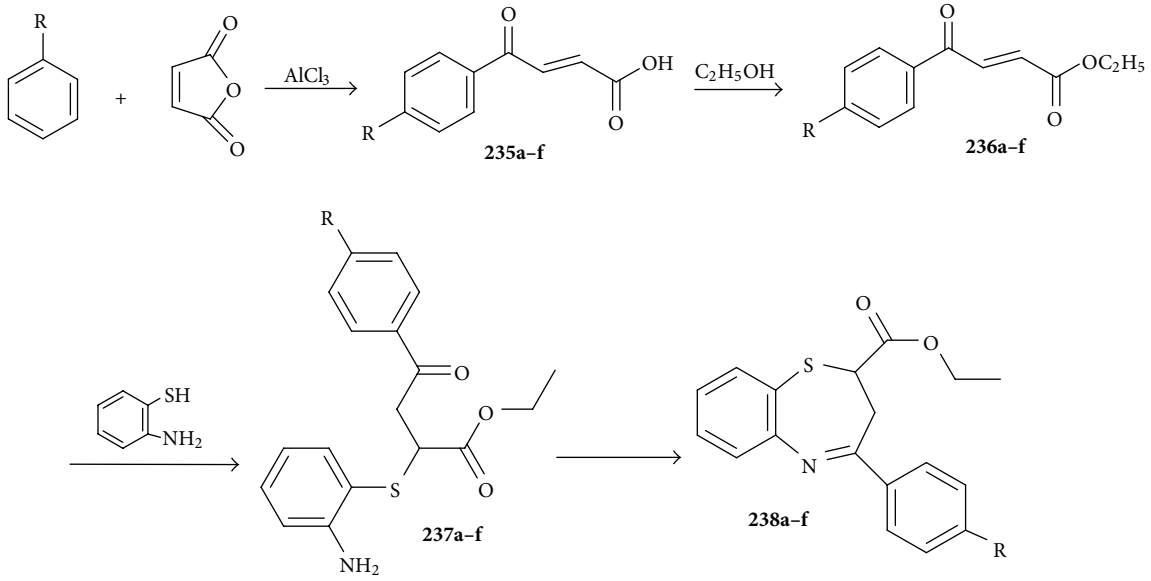


228	R^1	R^2	Yield (%)
(a)	Ph	4-MeC_6H_4	58
(b)	Pr	4-MeC_6H_4	68
(c)	Ph	Me	55

Reagents and conditions: (i) 1.1 equiv chloramine-T, 0.1 equiv PTAB, CH_2CN, r.t., 24 h
(ii) 1 equiv R^2SO_2Cl, 1 equiv Et_3N, CH_2Cl_2, r.t., 5 h



Scheme 46: Reaction of 2-(bromomethyl)-1-sulfonylaziridines with 2-aminothiophenol in THF in the presence of K_2CO_3: A regio- and stereocontrolled synthesis of *trans*-2-phenyl- and *trans*-4-(phenyl or propyl)-3-sulfonamido-2,3,4,5-tetrahydro-1,5-benzothiazepines.



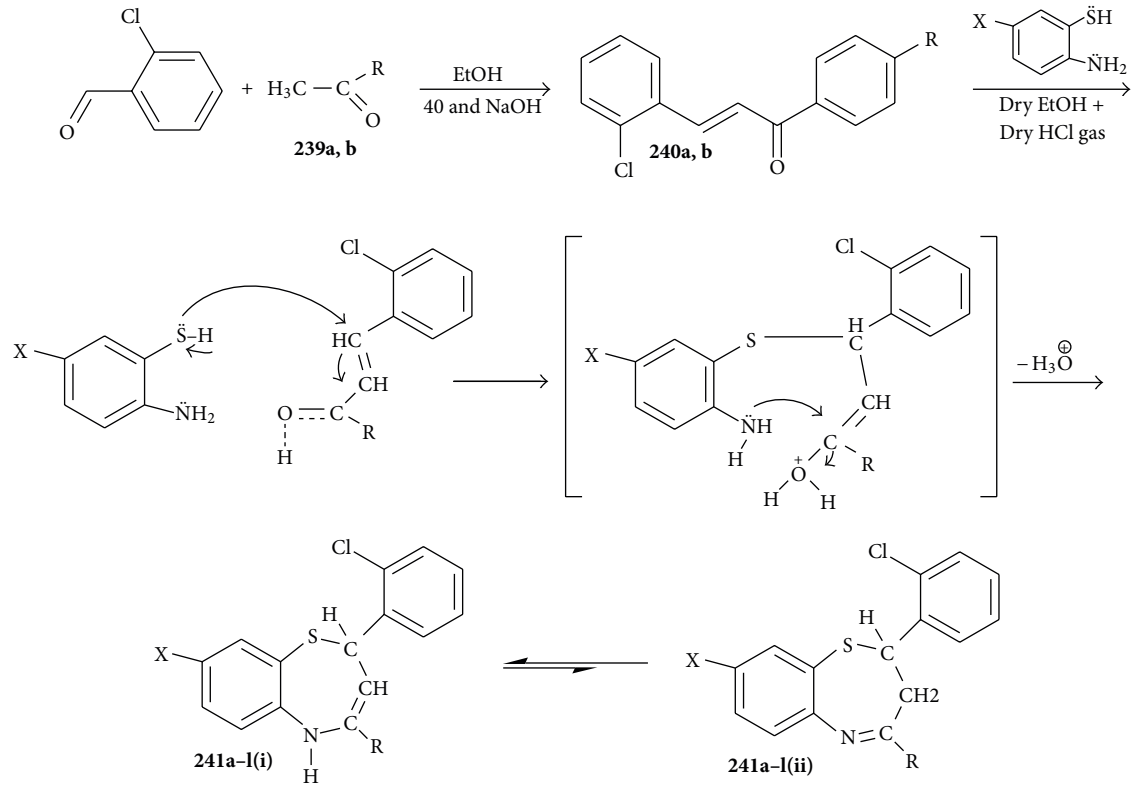
(a) R = H, (b) R = F, (c) R = Cl, (d) R = Br, (e) R = OCH_3, (f) R = CH_3

Scheme 47: Intramolecular cyclization through dehydration of ethyl 2-(2-aminophenylthio)-4-oxo-4-*p*-substitutes-phenyl-butanoate *via* heating.

was carried out by the condensation of *o*-aminothiophenol derivatives with methyl *trans*(±)-3-(4-methoxyphenyl)glycidate **246** in xylene at 160°C for 16–20 hours under nitrogen atmosphere. Treatment of **247** with dimethylsulphate afforded (±)*cis*-2-(4-methoxyphenyl)-3-methoxy-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones **248**, on treatment with chloroacetylchloride gave (±)*cis*-2-(4-methoxyphenyl)-3-methoxy-2,3-dihydro-1,5-benzothiazepin-4-(chloroacetyl)-ones **249**, which in turn afforded (±)*cis*-2-(4-methoxyphenyl)-3-methoxy-2,3-dihydro-1,5-benzothiazepin-4[5(4′-met-hylpiperazino-1′)acetyl]-ones **250** on reaction with *N*-methylpiperazine. Compounds **248** upon treatment with hexamethyldisilazane produced the corresponding trimethylsilyl derivatives **251** which when stirred with sugar, namely, *β*-D-ribofuranosyl-1-acetate-2,3,5-tribenzoate, in vaccuo at 155–160°C for 10 hours gave the corresponding nucleosides **252** [64, 65] (Scheme 50).

3.1.51. Multicomponent Reaction (MCR) of the Intermediates Benzylidenepyrazolinones with o-Aminothiophenol under Microwave Irradiation Using Montmorillonite K10 and through a Neat Reaction. Montmorillonite K10 is the most adaptable support for synthesizing the substituted benzothiazepines **257**, since a comparatively higher yield was achieved in a shorter time. The reaction has also been performed under neat conditions under microwave irradiation, where 2-phenyl-benzothiazole **260** was formed exclusively instead of the expected product pyrazolo[4, 3-*c*][1, 5]benzothiazepines **257**. When the same reaction was carried by heating **255** and aminothiophenol derivatives in EtOH and CH_3COOH low yield (15%) of products **257** was obtained instead of **259.** The formation of **257** was explained by involving the intermediacy of **256** instead of **258**. The mechanistic pathway of the reaction of benzylidenepyrazolinones **255** with aminothiophenol derivatives involves the formation of intermediate Michael adduct **256** *via* nucleophilic attack of the sulphydryl group on the *β*-carbon atom of the double bond of **255** which is rendered electrophilic due to vinyl-carbonyl conjugation (i.e., when substituents are present in an *α*,*β*-unsaturated ketone, only the nucleophilic addition of the mercapto group to the *β*-carbon atom takes place, followed by condensation of the carbonyl group with the aromatic primary amine to give a seven-membered ring system) and leads to the formation of the benzothiazepines **257**. Formation of intermediate **256** was confirmed by its isolation during the course of the reaction. It was also synthesized separately using isopropanol and their further conversion to final product and was found to be identical with benzothiazepine **257** synthesized using montmorillonite KSF. Formation of intermediate **256** rules out the possibility of the formation of product **259.**

In order to develop a facile procedure for the synthesis of **257**, it was carried out the improved synthesis of key intermediates **255a–c** in solvent-free conditions (neat) under microwave irradiation by irradiating a mixture of *p*-substituted benzaldehyde **254a–c** and 3-methyl-1-phenyl-2-pyrazolin-5-one **253** for 1–2 min to give **255a–c**. Therefore, it was used as such for further reaction with 2-aminothiophenol derivatives. Hence, this condition was extended for one-pot synthesis of **257** but surprisingly, the product isolated was identified as 2-phenyl-benzothiazole **260** instead of the expected benzothiazepine **257**. The formation of **260** can be explained by the mechanism which involved losses of pyrazolone moiety **253** from the intermediate **256**. Intramolecular



241	X	R	241	X	R
(a)	F	4-ClC_6H_4	**(g)**	F	2-C_4H_3S
(b)	Cl	4-ClC_6H_4	**(h)**	Cl	2-C_4H_3S
(c)	Br	4-ClC_6H_4	**(i)**	Br	2-C_4H_3S
(d)	CH_3	4-ClC_6H_4	**(j)**	CH_3	2-C_4H_3S
(e)	OCH_3	4-ClC_6H_4	**(k)**	OCH_3	2-C_4H_3S
(f)	OC_2H_5	4-ClC_6H_4	**(l)**	OC_2H_5	2-C_4H_3S

Scheme 48: Reactions of 3-(2-chlorophenyl)-1-(4-chlorophenyl)-2-propenone and 3-(2-chlorophenyl)-1-(2-thienyl)-2-propenone with 5-substituted-*o*-aminothiophenol derivatives in the presence of dry HCl gas and in dry ethanol.

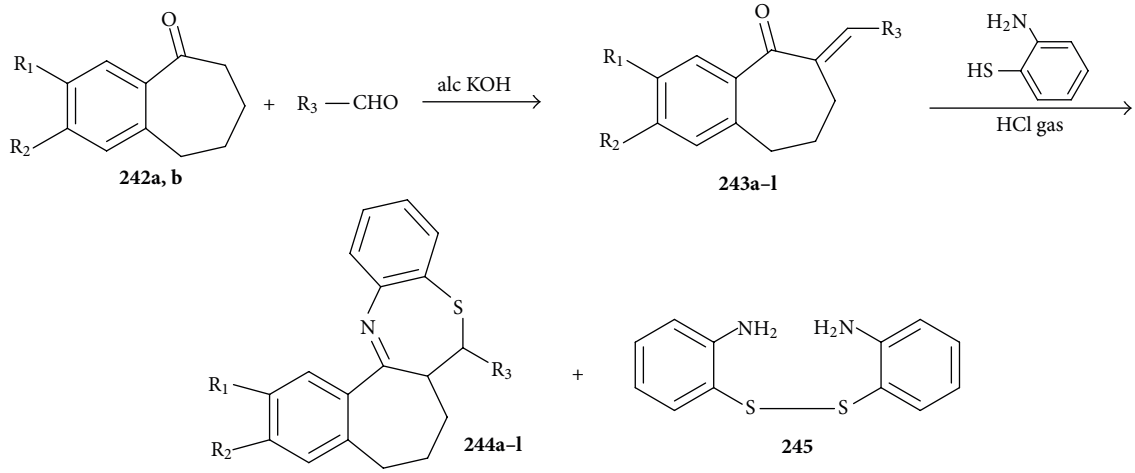
nucleophilic attack by a lone pair of nitrogen on the electrophilic carbon in (**261**) leads to the dihydro intramediate **262**, which is readily oxidized to the corresponding 2-arylbenzothiazoles **260**. The reaction was investigated also *via* MCR of **253**, **254**, and aminothiophenole derivatives under microwave irradiation using montmorillonite K10 and through a neat reaction. The results showed the formation of the pyrazolo[4, 3-*c*][1, 5]benzothiazepines **259** under microwave irradiation, in low yield, coupled with inorganic supports and the synthesis of 2-phenyl-benzothiazole **260** in neat conditions.

Finally, the results obtained under microwave irradiation were compared to conventional heating. The reaction in the case of compounds **257a** has been carried out using a preheated oil bath under the same conditions as under microwaves (time, temperature, vessel, and solid support). It has been found that reactants remained unchanged up to 7 min, while traces of mixture of product were obtained when the reaction time was extended to 7-8 h [66] (Scheme 51).

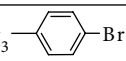
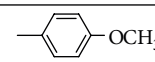
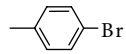
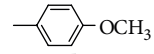
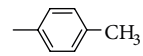
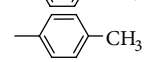
4. Miscellaneous Approaches

4.1. Solid-Phase Synthesis of 3,5-Disubstituted 2,3-Dihydro-1,5-benzothiaepin-4(5H)-ones. A synthetic pathway to benzothiazepines was described. Starting with a nucleophilic aromatic substitution of the benzoic acid **263** after immobilization of **264**. The nitro group was reduced by tin (II) chloride. Reductive alkylation of **265** gave **266**, which in turn reacted with aldehydes **267** and sodium cyanotrihydroborate **268** to afford the secondary anilines **269**. Intramolecular cyclisation formed the 3,5-disubstituted 2,3-dihydro-1,5-benzothiaepin-4(5*H*)-ones **270**. In this pathway, *N*-*α*-Fmoc-*S*-trityl-l-cysteine coupled to *p*-methylbenzhydryl amine resin, the trityl group was cleaved and the benzoic acid **263** was connected to give **271**.

A similar pathway to benzothiazepines was described previously [62]. *N*-*α*-Fmoc-*S*-trityl-l-cysteine was coupled to *p*-methylbenzhydrylamine resin, the trityl group was cleaved and the benzoic acid **263** was connected. The protected amine



Synthesis of 1,5-benzothiazepine derivatives **244a-l.**

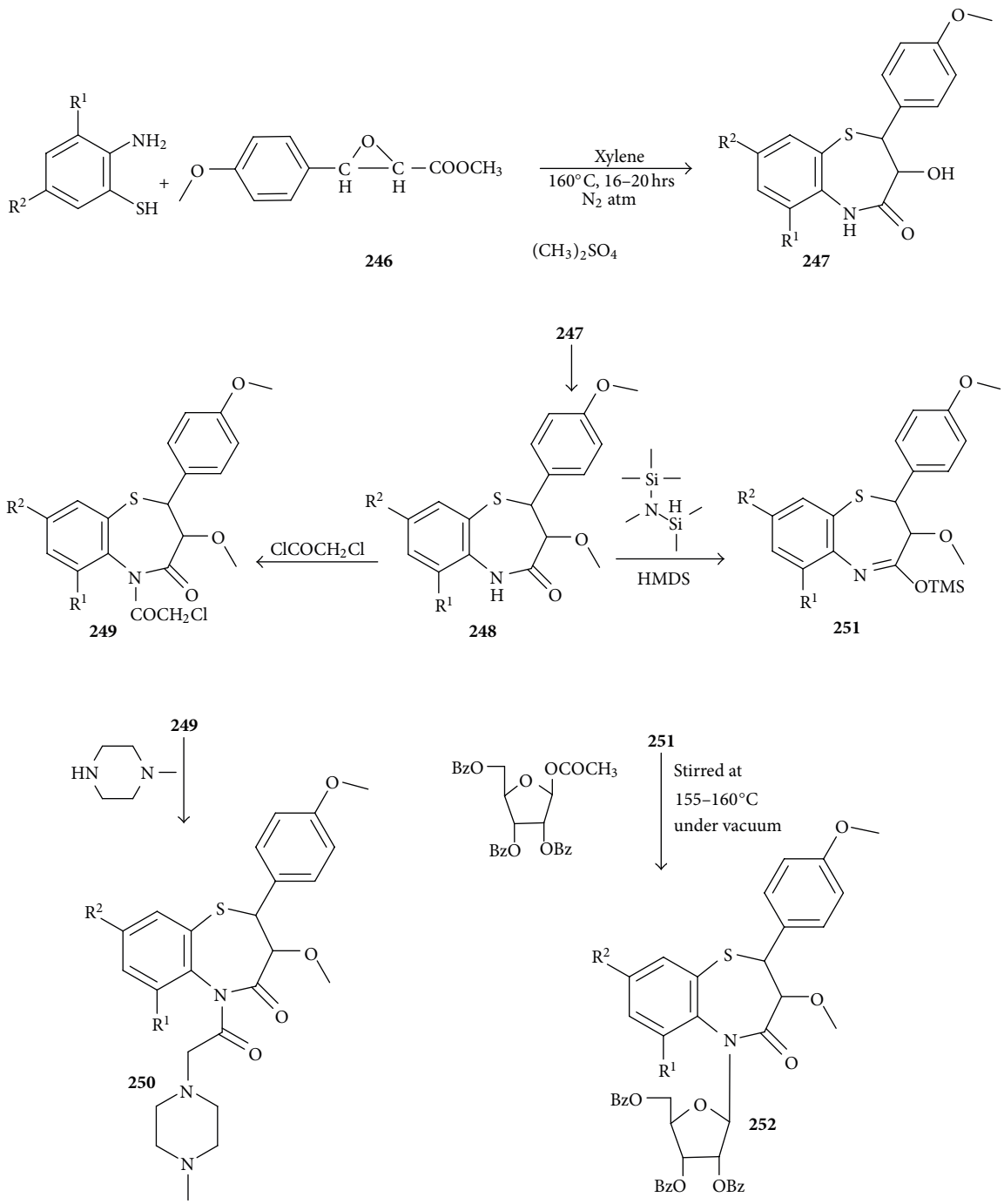
243,244	R_1	R_2	R_3	243 ,244	R_1	R_2	R_3
(a)	CH_3	CH_3		**(g)**	CH_3	CH_3	
(b)	CH_3	H		**(h)**	CH_3	H	
(c)	CH_3	CH_3		**(i)**	CH_3	CH_3	
(d)	CH_3	H		**(j)**	CH_3	H	
(e)	CH_3	CH_3		**(k)**	CH_3	CH_3	
(f)	CH_3	H		**(l)**	CH_3	H	

Scheme 49: Reactions of 6-arylidene-2,3-dimethyl/3-methyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-ones with *o*-aminothiophenol in dry (EtOH/HCl gas).

272 was deprotected and reductively alkylated. Cyclization of **273** resulted in the benzothiazepine skeleton **274**. The nitro group was reduced and coupled to the carboxylic acid [62, 67, 68] (Scheme 52).

4.2. Intramolecular Acylation of 1-(2-Carboxymethylthiophenyl)-2H-imidazol-2-ones in Polyphosphoric Acid. The starting benzothiazolones **276a** and **b** were obtained by alkylation of 2(3*H*)-benzothiazolones **275a** and **b** with chloroacetone in DMF at room temperature in the presence of dry K_2CO_3 and benzyltriethylammonium chloride (TEBA-Cl). Under these conditions, the alkyl derivatives **276a** and **b** were prepared for a more short time and in higher yields. Imidazolones **277a–k**, were obtained as a result of a ring transformation of 3-(2-oxopropyl)-2(3*H*)-benzothiazolones **276a** and **b** upon treatment with primary amines. In this case, the reaction was carried out in aqueous media, instead of perchloric acid, using 6–10 fold excess of the amine. To prevent a possible partial oxidation of the thiol group to disulfide, the products **277a–k** were immediately used in the next step without isolation and further purification. Alkylation reaction of **277a–k** with chloroacetic acid proceeded smoothly upon reflux in aqueous NaOH for 30–60 min. The resulting 1-(2-carboxymethylthiophenyl)-2*H*-imidazol-2-ones **278a–k** are stable compounds and were isolated with good to excellent yields (63–86%). Intramolecular acylation of compounds **278a–k** in polyphosphoric acid (PPA) at 110–120°C gave benzo[*b*]imidazo[1, 5-*d*][1, 5]thiazepines **279a–k** in 47–83% yield. The intramolecular acylation, described in this work, is a convenient and easily adjustable method for the synthesis of 1,5-benzothiazepines, containing an annelated imidazole ring substituted at 2-, 3-, or 5-position [69] (Scheme 53).

4.3. Reactions of Azirinobenzothiazine with HBr (Heating) or with Trifluoride Etherate (at Room Temperature). Azirinobenzothiazine **281** was synthesized *via* cycloaddition of dichlorocarbene (generated by alkaline hydrolysis of chloroform or thermocatalytic decomposition of sodium trichloroacetate) to the C=N double bond of 3-phenyl-2*H*-1,4-benzothiazine **280**. On heating **281** in concentrated

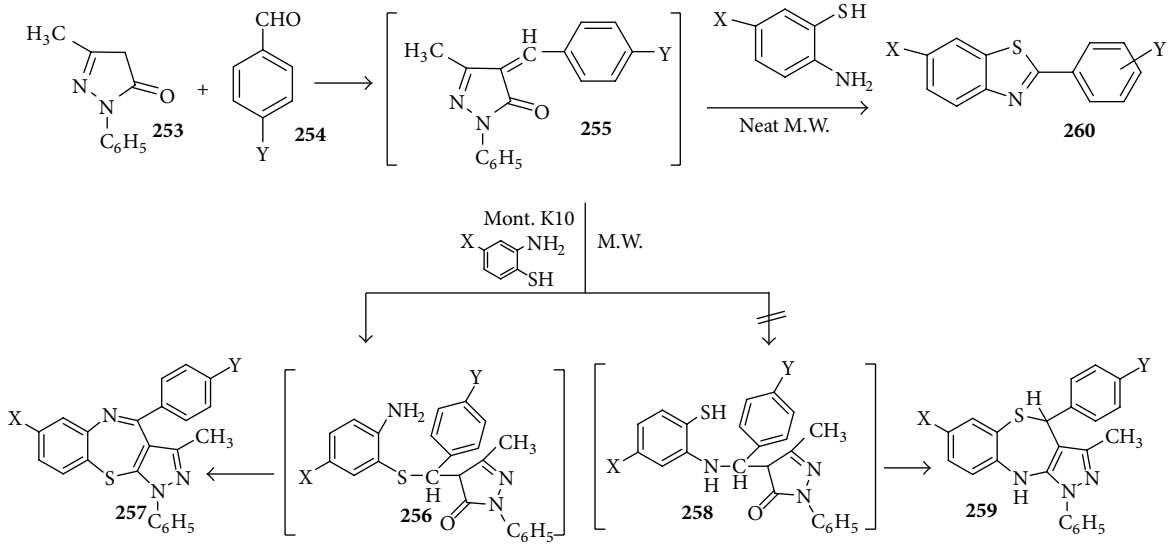


2-Aminobenzenethiol derivatives, **247–252**: (**a**) $R^1 = H$, $R^2 = OCH_3$; (**b**) $R^1 = OCH_3$, $R^2 = H$

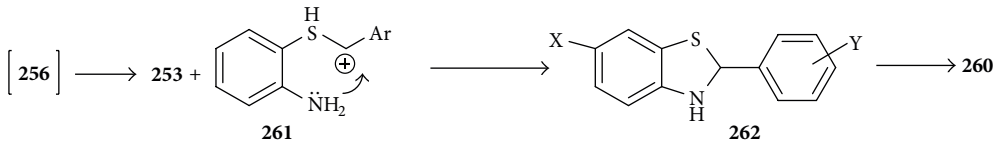
Scheme 50: Thermal condensation of *o*-aminobenzenethiol derivatives with methyl *trans*(±)-3-(4-methoxyphenyl)glycidate in xylene.

hydrobromic acid, the 3-bromodichloromethyl derivative of benzoxazine **282** was obtained as the main product (45% yield) together with the product of ring enlargement 1,5-benzothiazepine **283** in 5% yield. This finding attracted the interest to look for reaction conditions for the transformation of azirino[*c*][1, 4]benzoxazine and benzothiazine systems into derivatives of 1,5-benzoxaze-pine and benzothiazepine.

The azirinobenzothiazine **281** on reaction with boron trifluoride etherate at room temperature gave the imidoyl chloride **284**. This imidoyl chloride hydrolyzed more easily under purification on silica gel forming [1, 5]benzothiazepinone **285**. After chromatography on silica gel, 28% of the dichlorobenzo[1, 5]thiazepine **284** and 44% of the monochlorobenzo[1, 5]thiazepine **285** were isolated; whereas



Y: **254a** = OCH_3; **254b** = Cl; **254c** = H
X: 2-aminothiophenol derivatives and **257**: (**a**) = H; (**b**) = OCH_3; (**c**) = CH_3; (**d**) = Cl; 2-aminothiophenol derivatives = Br; (**f**) = OC_2H_5
X: **260**: (**a**) H and Y = Cl; (**b**) X = OCH_3 and Y = OCH_3; (c) X = H and Y = H



Pyrazolo[4,3-*c*][1,5]benzothiazepines **257**and2-phenyl-benzothiazole **260**

Compound	X	y	Time (min)	Yield [(a)] (%)	Rf [(b)]
257 (a)	H	H	6	90	0.81
(b)	H	Cl	7	80	0.72
(c)	OCH_3	OCH_3	8	85	0.76
(d)	OC_2H_5	OCH_3	9	80	0.82
(e)	Cl	OCH_3	8	82	0.79
(f)	Br	OCH_3	7	88	0.81
(g)	CH_3	Cl	6	80	0.88
(h)	Cl	Cl	7	76	0.75
(i)	CH_3	OCH_3	7	89	0.71
260 (a)	H	Cl	6	89	0.83
(b)	OCH_3	OCH_3	7	87	0.82
(c)	H	H	7	90	0.79

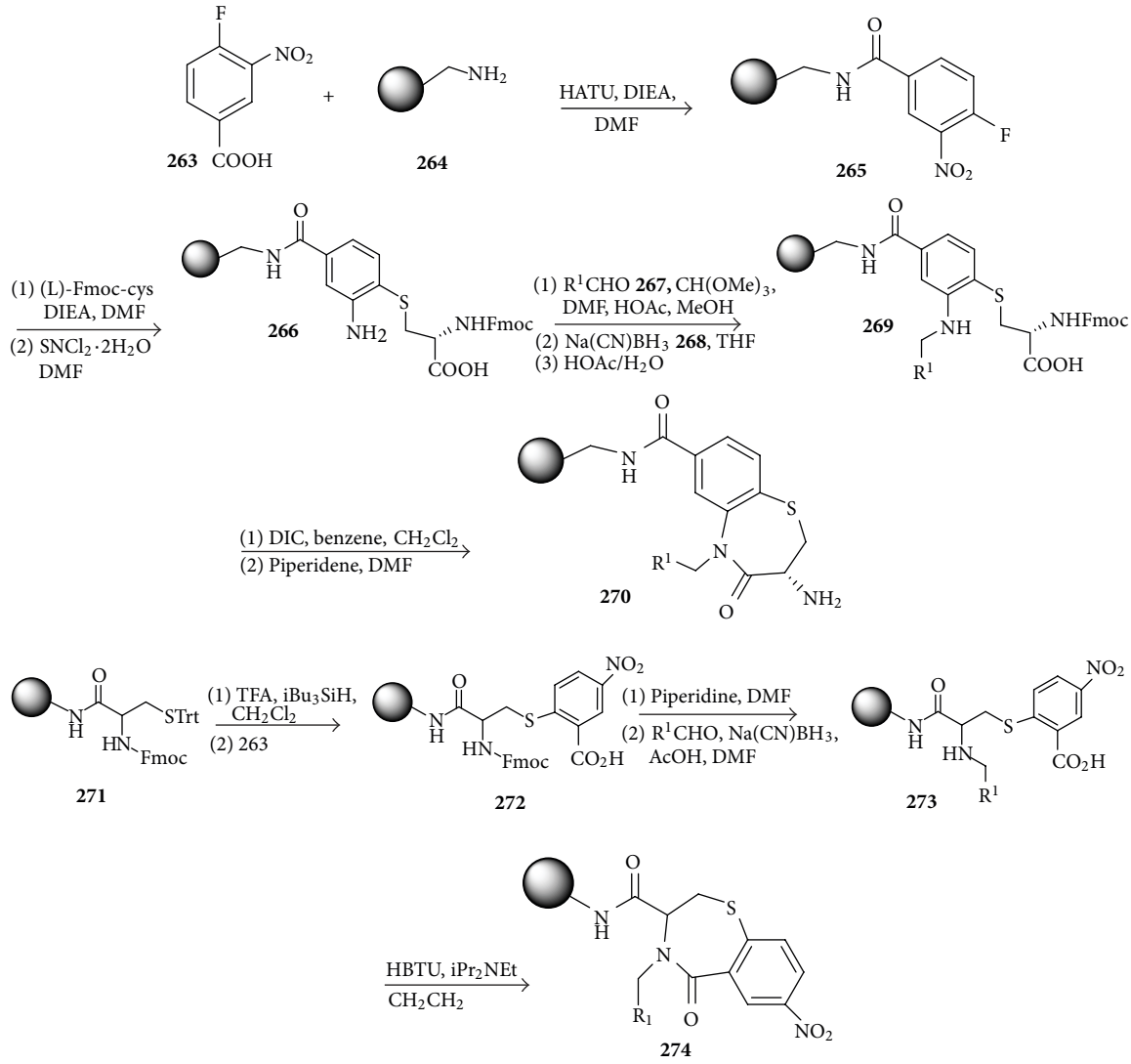
[(a)] Yield of the isolated products. [(b)] Using solvent system benzene : ethyl acetate (8 : 2)

Scheme 51: Multicomponent reaction (MCR) of the intermediates 4-benzylidene-1,3-disubstituted-1*H*-pyrazol-5(4*H*)-ones **255** with *o*-aminothiophenol under microwave irradiation using montmorillonite K10 and through a neat reaction.

chromatography on alumina gave 83% of compound **284** and 13% of compound **285**.

The benzothiazepine **284** contains two chlorine atoms, which could potentially be used for its modification *via* reactions with nucleophiles. When compound **284** was heated with sodium methoxide in methanol, and it was smoothly transformed into the corresponding methoxy derivative **286**. Chloride **284** reacted also with morpholine to give amidine **287** in good yield [70, 71] (Scheme 54).

4.4. Reactions of 4-Methoxy-α-[(4H-pyrrolo-3-pyridyl)thio]-phenyl Acetic Acid with Phosphorus Pentachloride. 4-Aminopyridine reacted with pivaloyl chloride at 0°C in the presence of Et_3N to form 4-pivaloylaminopyridine **288** in high yield. Double lithiation of **288** using 2.5 M *n*-butyllithium produced a white precipitate of the dilithio derivative. Reaction of this species with the electrophile tetraisopropylthiuram disulfide (TITD) produced 3-(*N*,*N*-diisopropyldithiocarbamato)pyridine **289** in good yield (87%). Attempted removal of the pivaloyl group using 5 M-HCl solution produced a 2-*tert*-butylthiazolo[5, 4-*c*]pyridine **290** in 99% yield. The subsequent alkaline hydrolysis of **290** produced the disulfide **291**. The 1,2-bis(4-(1*H*-pyrrol-1-yl)pyridin-3-yl)disulfane **292** was prepared by reaction of 2,5-dimethoxytetrahydrofuran with bis(2-amino-4-pyridyl)disulfide **291**. The disulfane **282** was

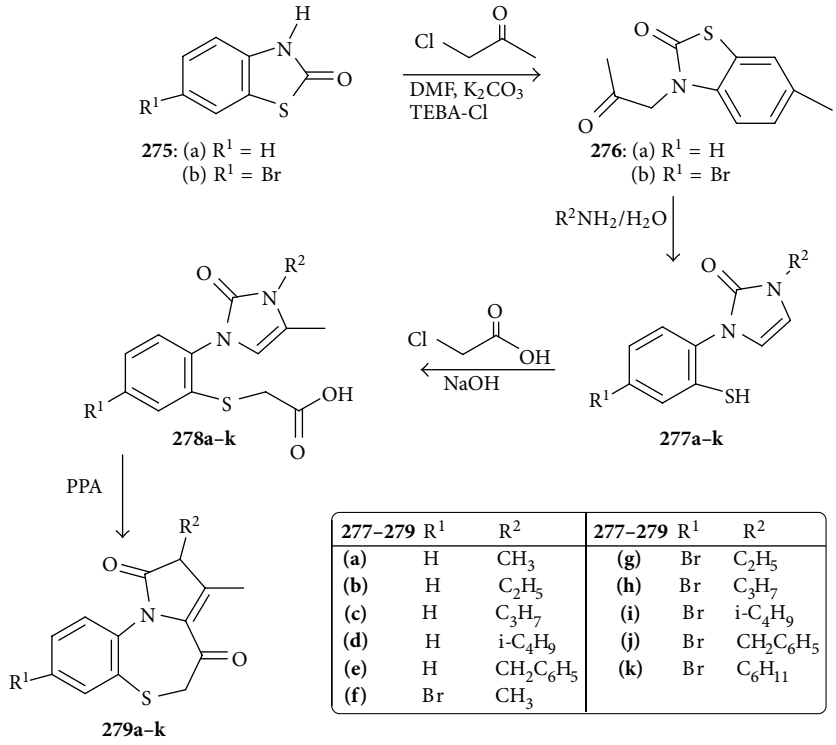


Scheme 52: Solid-phase synthesis of 3,5-disubstituted 2,3-dihydro-1,5-benzothiaepin-4(5*H*)-ones.

reduced with $NaBH_4$ in refluxing ethanol to give 3-mercapto-4*H*pyrrolopyridine and the latter subsequently reacted with α-bromo-4-methoxyphenylacetic acid ethyl ester (obtained from 4-methoxyphenylacetic acid by an esterification reaction with absolute ethanol containing a catalytic amount of concentrated H_2SO_4, and then bromination with *N*-bromosuccinimide) to give ethyl 2-(2-(1*H*-pyrrol-1-yl)phenylthio)-2-(4-methoxyphe-nyl) acetate **293**. Hydrolysis of ester group in **293** with 5% NaOH solution afforded 4-methoxy-α-[(4*H*-pyrrolo-3-pyridyl) thio] phenyl acetic acid **294**. Intramolecular cyclization of the acid **294** using phosphorus pentachloride gave the target compound: 2-(4-Methoxyphenyl)pyrrolo[2,1-*d*]pyrido[2,3-*c*][1, 5]thiazepine-3(2*H*)-one **295** [72] (Scheme 55).

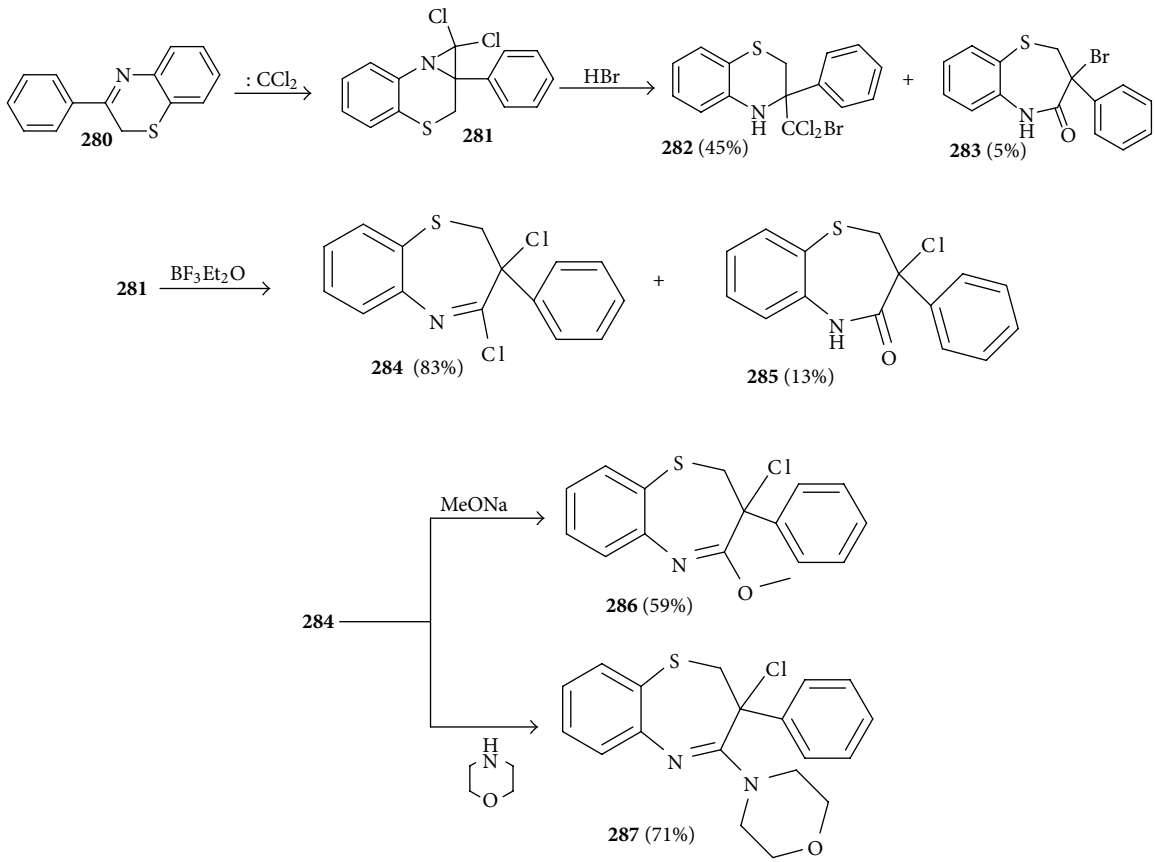
4.5. Reaction of (E)-1-(2-Hydroxyphenyl)-3-(p-substituted phenyl)prop-2-en-1-ones with 1-Amino-2-mercapto-5-phenyl-1,3,4-triazole in the Presence of a Catalytic Amount of Sodium Acetate in DMSO. One pot reaction of chalcones **296a–f** under microwave irradiation (6–8 min, at 500 W with short interruptions of 30 sec to 1 min to avoid an excessive evaporation of the solvent) with 1-amino-2-mercapto-5-phenyl-1,3,4-triazole in the presence of a catalytic amount of sodium acetate in DMSO, underwent heterocyclization, afforded the corresponding 1,5-thiadiazepines **297a–f** in good yields (92–80%). The formation of **297** probably involves the intermediates (**298**) which could produce **297a–f**. The formation of the condensed heterocyclic compounds **297** by the dehydration of (**298**) could be favorable in a nonaqueous medium. A dipolar transition state is involved in the formation of intermediates (**298**) by the 1,2- and 1,4-addition to the carbonyl group and to the β-carbon atom of the α,β-unsaturated carbonyl system, followed by cyclization to give title 1,5-benzothiazepine **297** [73] (Scheme 56).

4.6. Synthesis of Indolo[3,2-b]-1,5-benzothiazepine-ones from Indoleanilides Substituted at C-2 and at C-3. Indoleanilides substituted at C-2 (**300**, **302**, **304**, **306**): indole-2-carboxylic

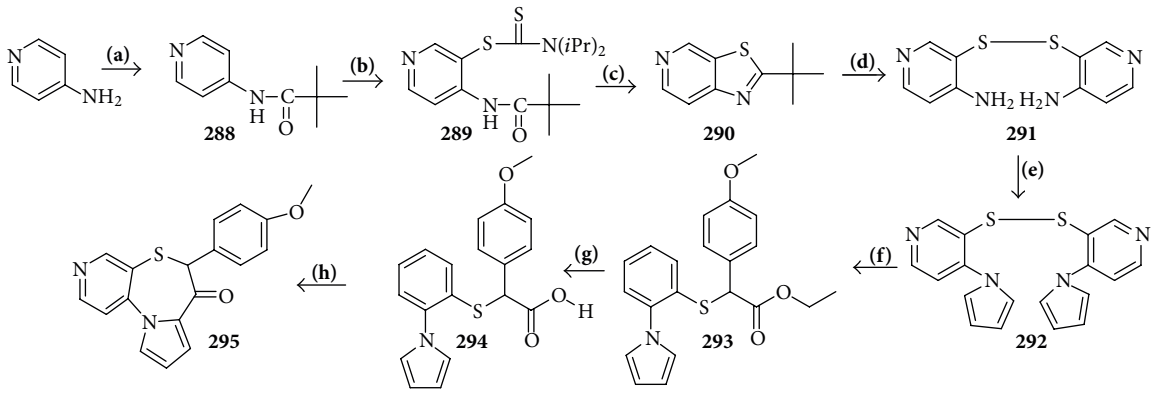


277–279	R^1	R^2	277–279	R^1	R^2
(a)	H	CH_3	**(g)**	Br	C_2H_5
(b)	H	C_2H_5	**(h)**	Br	C_3H_7
(c)	H	C_3H_7	**(i)**	Br	i-C_4H_9
(d)	H	i-C_4H_9	**(j)**	Br	$CH_2C_6H_5$
(e)	H	$CH_2C_6H_5$	**(k)**	Br	C_6H_{11}
(f)	Br	CH_3			

Scheme 53: Intramolecular acylation of 1-(2-carboxymethylthiophenyl)-2*H*-imidazol-2-ones in polyphosphoric acid.

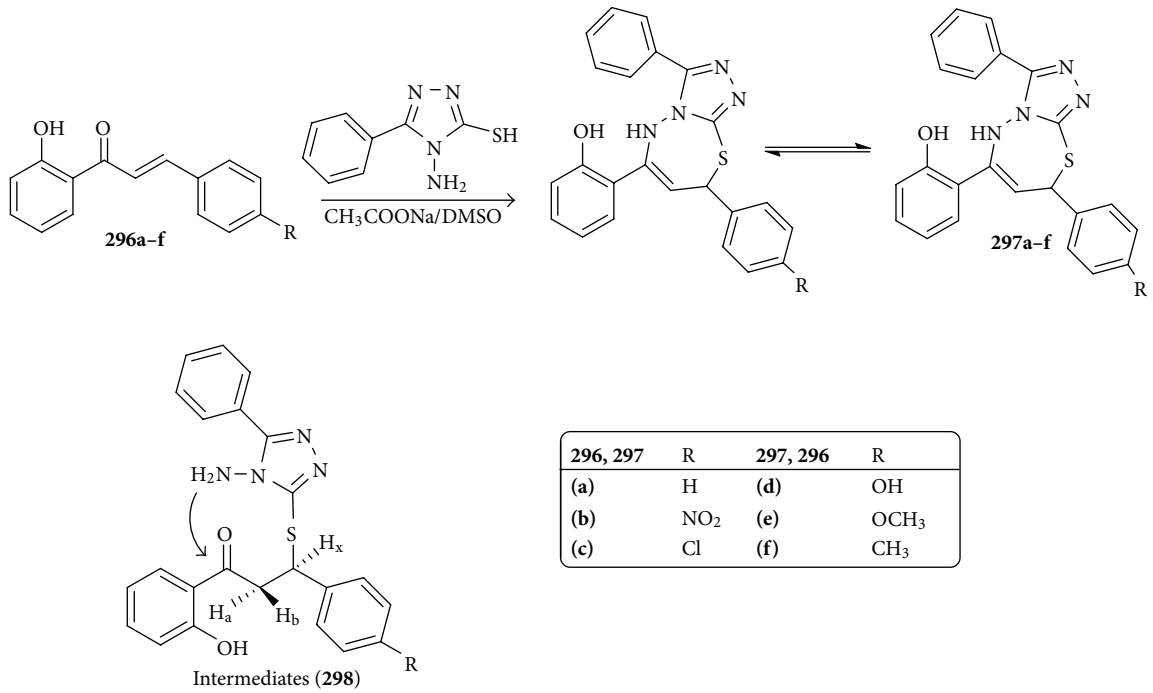


Scheme 54: Reactions of azirinobenzothiazine with HBr (heating) *or* with trifluoride etherate at room temperature.



Reagents and conditions: (**a**) pivaloyl chloride, Et_3N, anhydrous CH_2Cl_2, 0°C; (**b**) TITD, 2.5M *n*-butyllithium, −78°C, anhydrous THF; (**c**) 5 M-HCl, reflux; (**d**) 5MNaOH, solid NaOH, reflux; (**e**) 2.5-dimethoxytetrahydrofuran, glacial acetic acid,110°C; (**f**) (i) $NaBH_4$, absolute EtOH, reflux, (ii) a-bromophenyl acetic acid ethyl ester, EtOH, rt; (g) 5% NaOH, MeOH, MeOH/THF (1 : 1), rt; (**h**) PCl_5, anhydrous CH_2Cl_2, rt, 60°C

Scheme 55: Reactions of 4-methoxy-α-[(4*H*-pyrrolo-3-pyridyl)thio]phenyl acetic acid with phosphorus pentachloride.



296, 297	R	297, 296	R
(a)	H	(d)	OH
(b)	NO_2	(e)	OCH_3
(c)	Cl	(f)	CH_3

Scheme 56: Reaction of (*E*)-1-(2-hydroxyphenyl)-3-(*p*-substituted phenyl)prop-2-en-1-ones with 1-amino-2-mercapto-5-phenyl-1,3,4-triazole in the presence of a catalytic amount of sodium acetate in DMSO.

acid chloride and a 2-(alkylthio) aniline produced sulfides **299a–c** in modest yields. Problems have been reported with reactions of indole carboxylic acids with thionyl chloride and use of the unstable acid chloride (and consequent low yield of amide) could be avoided by trimethylaluminum-catalyzed condensation of 2-(alkylthio)anilines and ethyl indole-2-carboxylate. For example, **299a** was obtained in 92% yield by this approach. The method selected was typically based on solubility of the starting sulfide in the oxidation medium.

Monoalkylated compounds **302ab** bearing a methyl substituent on the amide nitrogen were prepared, on replacing the aniline component with an *N*-methyl-2-(alkylthio) aniline followed by oxidation. Monoalkylated compounds bearing the methyl substituent on the indole **304ab** were prepared from alkylthioanilines and *N*-methylindole carboxylic

acid followed by oxidation. N,N'-Dimethylated compounds **306ab** were prepared by dialkylation of amides (**299ab**) by catalytic phase transfer methylation followed by oxidation. Sulfide **299c** decomposed under phase transfer conditions (retro-Michael) so compound **306c** was prepared in low yield by reaction of 1-methyl-1*H*-indole-2-carboxylic acid chloride with 3-{[2-(methylamino)-phenyl]thio}propanenitrile followed by oxidation. When the sulfoxides were subjected to cyclization conditions (either activation by electrophilic species (TFAA) or thermally (refluxing in chloroform or *p*-xylene)) clear patterns of reactivity emerged when the sulfoxides were cyclized. Conditions for cyclization were either thermal (refluxing in chloroform or *p*-xylene) or electrophilic activation (TFAA). In successful reactions, *tert*-butyl sulfoxide derivatives cyclize thermally in refluxing chloroform; whereas ethyl sulfoxide derivatives require higher temperatures (refluxing in *p*-xylene).

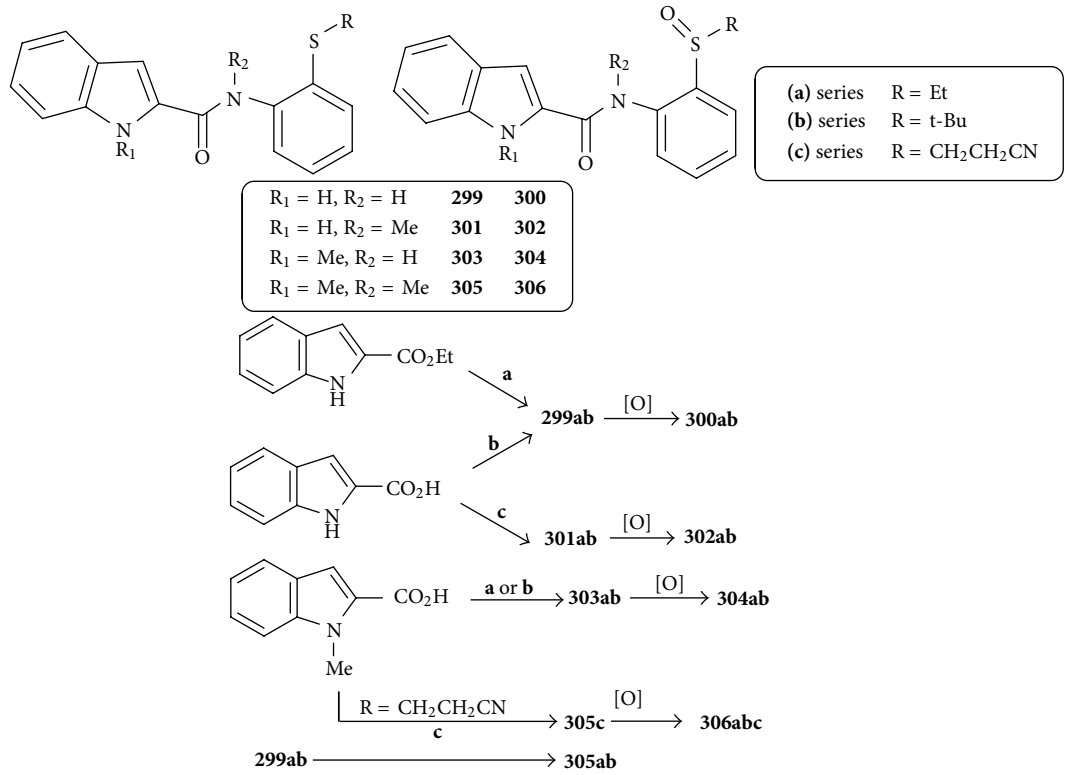
Compounds in which the amidic site is methylated (but still contain an indolic N–H) **302ab** cyclize both thermally and with TFAA activation to 10,11-dihydro-10-methyl-12H-indolo[3, 2-*b*]-1,5-benzothiazepin-11-one **307**. Dimethylated compounds **306abc** react to give 10,11-dihydro-10,12-dimethylindolo[3, 2-*b*]-1,5-benzothiazepin-11-one **308**. Due to competing side reactions, yields of **308** from 2-propanenitrile compounds were inferior to both ethyl and *tert*-butyl sulfoxides and were not pursued further. In addition, **308** was synthesized from **309**. Refluxing **309** in toluene using SiO_2 as catalyst gave **310**, which upon catalytic phase transfer dimethylation gave a product chromatographically and spectroscopically identical to the cyclisation product **308**. This clearly establishes the sites of attachment of the sulfur and carbonyl groups on the indole ring of the SES product. Catalytic phase transfer methylation of **307** also produced **308** (76%) confirming the structure of that product as well.

Indoleanilides substituted at C-3. Reproducibility problems were encountered with the reported preparation of 3-indole carboxylic acid while preparing **311a**, so the *tert*-butyl analogue **311b** was prepared directly from indole and 2-(*tert*-butylthio)aniline in the presence of tri-phosgene and pyridine in 33% yield. Methylation and oxidation provided **314b**. Cyclizations of sulfoxides **312a**, **314ab**, or the thio-compound **313ab** were conducted under both thermal activation and TFAA activation. The product obtained from heating **314a** under reflux for 15 h in *p*-xylene (67% yield after chromatography) proved to be identical to the benzothiazepine **308**, the cyclization product from the 2-substituted indole sulfoxide.

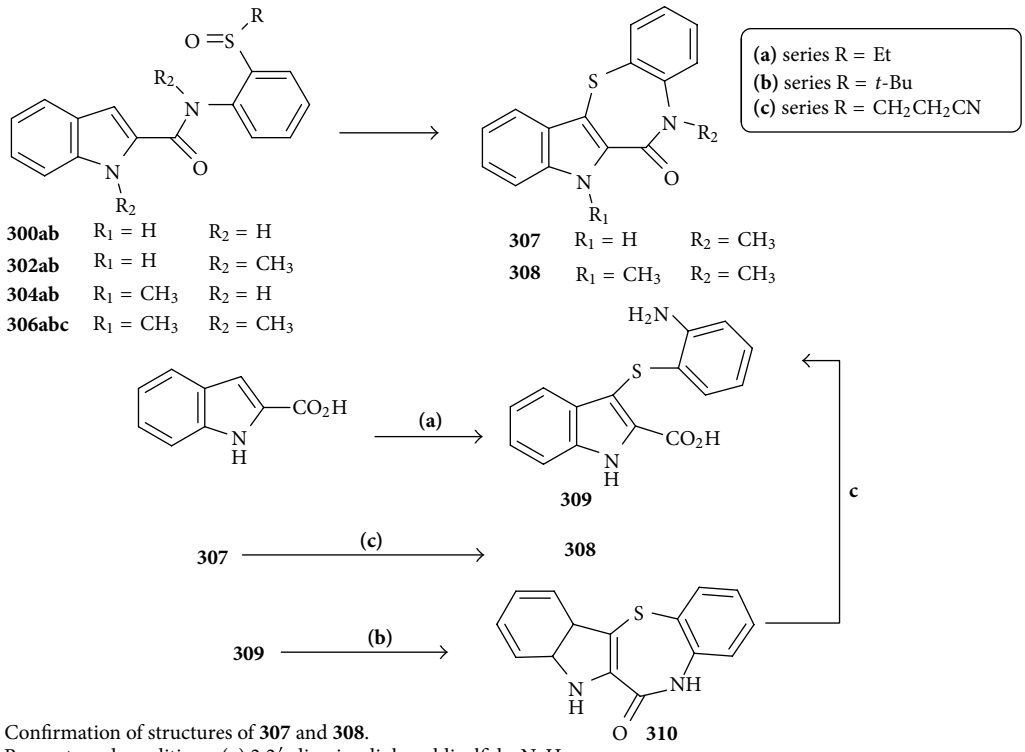
As a conclusion both 2- and 3-indoleanilides **306abc** and **314a** undergo cyclisation to produce the same product-indolo[3, 2-*b*]-1,5-benzothiazepin-11-one **308**. For the 3-indoleanilides, the possibility of indole substituent migration before or after cyclization was eliminated and a 3*H*-indolinium spirocyclic intermediate, with preferential migration of the amide-containing moiety from C-3 to C-2, *via* **315**-**316**-**317** is proposed to rationalize the rearrangement. Also, it was discovered that successful cyclisation in this series requires the absence of an amidic hydrogen in the compounds. The lack of cyclization of compounds containing an amidic hydrogen is attributed to N–H···O=S hydrogen bonding, a low energy trans-amide conformation, and a formidable rotational barrier to the *cis*-amide conformation, all of which enforce a molecular geometry that precludes the sulfur atom from achieving an orientation conducive to interaction with indole π-electrons. By extrapolation, if cyclized compounds containing an amidic hydrogen are synthetic targets, one should consider introducing an easily removable amidic alkyl substituent (e.g., benzyl) into the SES substrate [74] (Scheme 57).

4.7. Cyclization of 3-{5-[Anilino-2-(alkylamino)phenyl]sulfanyl}-propanoic Acids with 1,3-Dicyclohexylcarbodiimide (DCC) at r.t. in THF. N^1-(Alkyl)-2-(alkylsulfanyl)-N^4-phenyl-1,4-benzenediamines **319a–f** were prepared in 87–97% yields by treatment of *N*-4-[(alkyl)imino]-2,5-cyclohexadien-1-ylideneanilines **318a–c** with the corresponding R-mercaptoalkanoate esters. Also, 2*H*-1,4-benzothiazin-3(4*H*)-ones **320a–f** prepared in 89–97% yields by intramolecular cycloadditions of compounds **319a–f** on treatment with trifluoroacetic acid under reflux overnight. Alkyl 3-{[5-anilino-2-(alkyl-amino) phenyl]sulfanyl}-propanoates **321a–f** were obtained in 86–92% yields by treatment of *N*-4-[(alkyl)imino]-2,5-cyclohexadien-1-ylideneanilines **318a–c** with the corresponding β-mercaptoalkanoate esters. Cyclization of compounds **321a–f** by heating with trifluoroacetic acid at 70°C was attempted. Compounds **321a–f** failed to provide the desired cyclized benzothiazepines **322a–f** under these reaction conditions. Refluxing of compounds **321d–f** in chlorobenzene for 2 days led only to recovery of the starting materials. When Decalin was used as a solvent, decomposition of the starting materials occurred after heating at 190°C for 3 days. The synthesis of benzothiazepinones was tried by treating benzoquinone diimines **318a–c** with 3-mercaptopropionic acid. It was envisioned that once the addition products, 3-{[5-anilino-2-(alkylamino) phenyl]sulfanyl}-propanoic acids **323a–c** were made, cyclization could be achieved upon addition of 1,3-dicyclohexylcarbodiimide (DCC). Intermediate compounds **323a–c**, were isolated (but characterized only by ^{1}H NMR) and further used in the final cyclization step to obtain the target benzothiazepines **322a–c**. Treatment of the intermediates **323a–c** with DCC and subsequent purification by flash column chromatography gave the desired benzothiazepines **322a–c** in 81–97% yields [75] (Scheme 58).

4.8. Ring-Closure Reactions between α,β-Unsaturated Ketones and the Intermediate Samarium Diiodide (Kagan Reagent). Ring-closure reactions between α,β-unsaturated ketones and intermediates samarium diiodide (Kagan reagent) **325** (prepared from bis(*o*-nitrophenyl)disulfide **324** and SmI_2) took place readily to afford 2,3-dihydro-1,5-benzothiazepines **326**. It was found that chalcones are more reactive toward the new anionic species **325** than any other α,β-unsaturated ketones. It must be noted that *o*-aminothiophenols were less reactive toward aldehydes than the intermediates **325** [76] (Scheme 59).

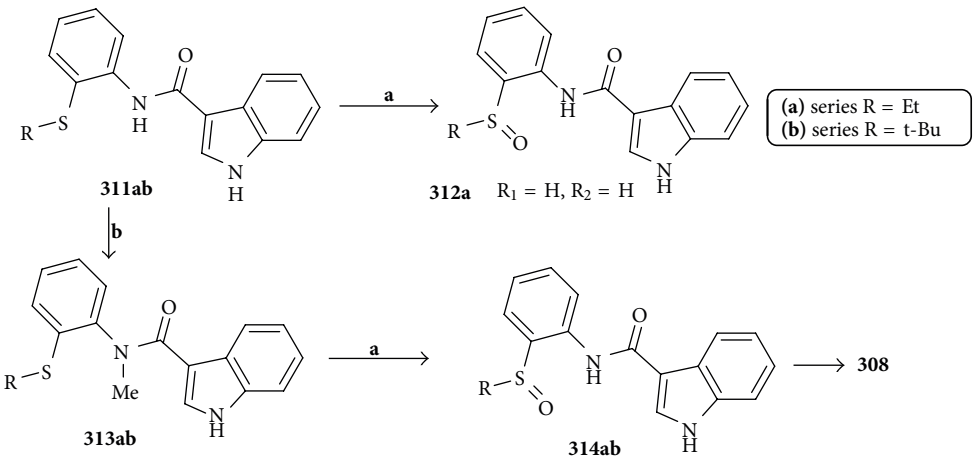


Synthesis of 2-indoleanilides.
Reagents and conditions (compound number,% yield): (a) 2-ethylthioaniline, $AlMe_3$, toluene, reflux(**299b** 92%,**303a** 84%); (**b**) SOCl , Et_2O, 2-(alkylthio)aniline, rt (**299a**, 32%, **299b** 71%, **303b** 59%); (**c**) $SOCl_2$, Et_2O, N-methyl-2-(alkylthio)aniline, rt (**301a** 38%, **301b** 79%, **305c** 27%); (d) 50% NaOH, CH_3I, n-Bu_4NHSO_4, toluene (**305a** 82%, **305b** 79%).

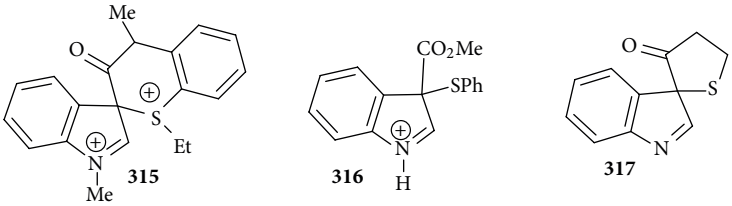


Confirmation of structures of **307** and **308**.
Reagents and conditions: (**a**) 2,2′-diaminodiphenyldisulfide, NaH, DMF (93%); (**b**) SiO_2, toluene, reflux (63%); (**c**) *n*- Bu_4NHSO_4, 50% NaOH, CH_3I, toluene, reflux [from **307** (76%), from 12 (89%)].

Scheme 57: Continued.



Preparation and SES reactions of 3-indoleanilides.
Reagents and conditions: (a) m-CPBA, CH_2Cl_2, − 10°C
(**312a** 96%, **314a** 72%, **314b** 49%); (b) *n*- Bu_4HSO_4, 50% NaOH, CH_3I, toluene, reflux (**313a** 90%, **313b** 73%).



A proposed mechanism for initial formation of a 3*H*-spirocyclic intermediate

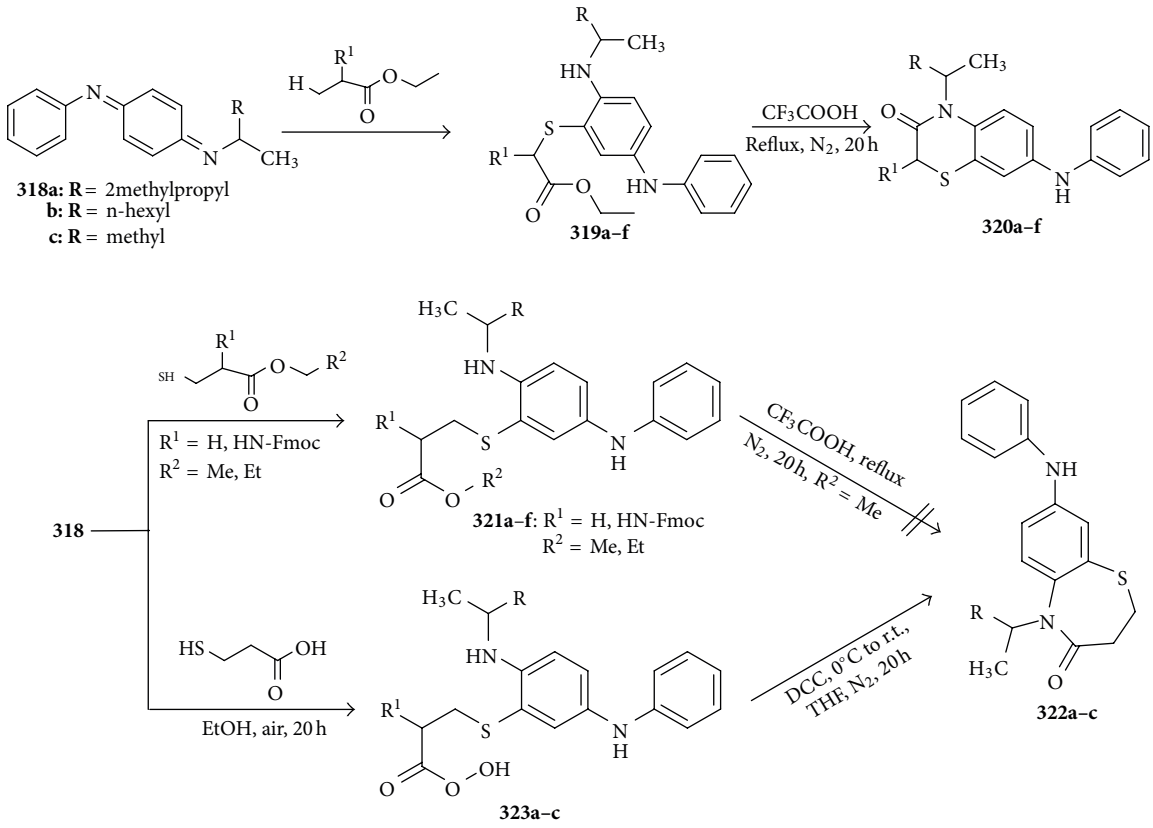
Scheme 57: Synthesis of indolo[3,2-*b*]-1,5-benzothiazepine-ones from indoleanilides substituted at C-2 and at C-3.

5. Reactions

5.1. Staudinger Reaction of 2,4-Disubstituted 2,3-Dihydro-1,5-benzothiazepines with Cyclohexanecarboxylic Chloride in the Presence of Triethylamine in Anhydrous Benzene. The reaction of 2-(4-chlorophenyl)-4-phenyl-2,3-dihydro-1,5-benzothiazepine **327a** with cyclohexanecarboxylic chloride in the presence of triethylamine when carried out using commercially available benzene as solvent afforded the amide **329a** and not the β-lactam derivative **328a** (<5% yield). Using sodium-dried benzene as solvent, the reaction also gave amide **329a** as the major product together with a 16% yield of β-lactam **328a** and some recovered 1,5-benzothiazepine **327a**. A longer reaction time of 8 h increased the yield of β-lactam **328a** to 27%; but with a more extended reaction time no further improvement of the yield was achieved. In the same way, the spirofused β-lactams **328b,c** (34–54%) and amides **329b,c** (16–38%) together with recovered starting materials were obtained from 1,5-benzothiazepines **327b,c**. The lower yields of β-lactams **328** in the current cases are possibly due to steric hindrance of the disubstituted ketene, penta-methyleneketene. A proposed reaction mechanism for the formation of amides **329** was suggested as follows. Imines **327** (R^1, R^2, R^3 = Ph, H, 4-XC_6H_4) reacted with pentamethyleneketene to form zwitterionic intermediates **A**, which undergo a conrotatory ring closure to form β-lactam derivatives **328**. The zwitterionic intermediates **A** was not completely converted into β-lactams and reacted with water during workup to generate hemiaminal intermediates **B**, which, in turn, underwent ring opening forming the amides **329**. Formation of β-lactams and amides is competitive in the Staudinger reaction with the weak electron-donating disubstituted ketene [77] (Scheme 60).

5.2. Ring Contraction of 1,5-Benzothiazepines. When 1,5-Benzothiazepins **330–339** were allowed to react with a mixture of acetic anhydride and pyridine afforded 3-acetyl-2,3-dihydro-2-phenyl-2-styrylbenzothiazoles **340–349** (83–61% yield) *via* ring contraction of the thiazepine ring. It is worth mentioning that the *ortho*-acetoxy group in the phenyl ring at position 2 of compounds **330–337** seemed to be without influence on the acetylation of the nitrogen atom and, therefore, on the course of the ring contraction leading to the formation of benzothiazoles **340–347**. The above mentioned 3-acetyl-2,3-dihydrobenzothiazoles appeared to be convenient substrates to get newer insights into the scope and limitation of the utility of the dimethyldioxirane for a chemoselective oxidation of the sulfur atom of compounds with various sites of oxidation. Therefore, when compounds **340, 344–353** were allowed to react with isolated dimethyldioxirane (DMD) (in acetone solution) their 1,1-dioxides **354–364** were obtained as sole isolable product (78–94% yield) in each case [78] (Scheme 61).

5.3. Reactions between 2,4-Disubstituted-2,3-dihydro-1,5-benzothiazepines and Ketenes. Reaction of benzothiazepines **365** and **366** in the presence of Et_3N showed different



Preparation of Alkyl 3-{[5-anilino-2-(alkylamino)phenyl]sulfanyl} propanoates (**321a–f**),3-[5-anilino-2-(alkylamino) phenyl]sulf anyl propanoic acid **323a–c** and 2,3-Dihydro-1,5-Benzothiazepin-4(5*H*)-ones (**322a–c**)

Entry	R	R^1	R^2	Yield (%)	Entry	R	R^1	Yield (%)
321(a)	2-Methylpropyl	H	Me	90	**322a**	2-Methylpropyl	H	85
(b)	*n*-Hexyl	H	Me	89	**b**	*n*-Hexyl	H	97
(c)	Me	H	Me	86	**c**	Me	H	81
(d)	2-Methylpropyl	HN-Fomic	Et	88	**323a**	2-Methypropyl	H	71
(e)	*n*-Hexyl	HN-Fomic	Et	90	**b**	*n*-Hexyl	H	63
(f)	Methyl	HN-Fomic	Et	92	**c**	Me	H	70

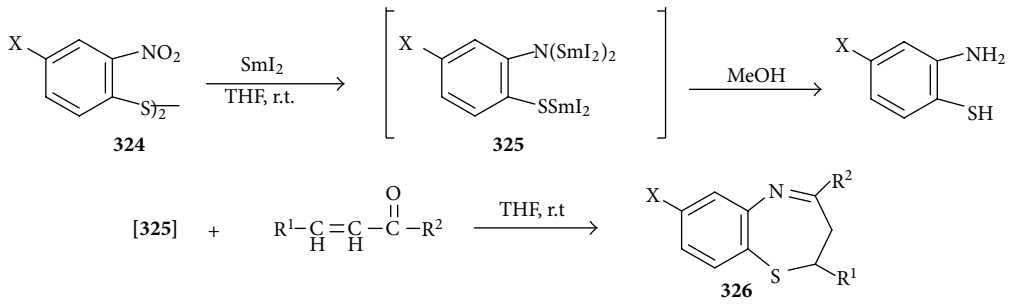
Scheme 58: Cyclization of 3-{[5-anilino-2-(alkylamino) phenyl]sulfanyl}-propanoic acids with 1,3-dicyclohexylcarbodiimide (DCC) at r.t. in THF.

reactivity with different substituents on **365** or **366**, and several different products at different reaction temperatures have been obtained.

When the reaction was carried out at room temperature, reaction of **365** and **366** produced **367** as the major product, except that $\mathbf{369_{Bb}}$ was obtained as the major product in the reaction of 2-methyl substrate $\mathbf{365_B}$ with dichloroacetyl chloride. However, the reaction gave very complicated products when carried out at refluxed temperature. The product is a mixture of **367**, **368**, and **369**, one or two of which are major products, and product **369** can only be obtained when reagent **366** is $\mathbf{366_b}$. Compounds **367, 368**, and **369** have been separated and characterized, among them, **368** and **369** are new types of compounds. Compound $\mathbf{367_{Da}}$ was further characterized by X-ray diffraction analysis.

At room temperature, reaction of chloroacetyl chloride (**366a**) with $\mathbf{365_{A-F}}$, followed by the addition of triethyl amine, gave the expected product $\mathbf{367_{(A-F)a}}$. All of these compounds were in the form of white crystal. The chemical shifts of the three protons on the seven membered ring and the corresponding coupling constants are different.

When the 2-position has a methyl group, the NMR signal of proton 4-H is shifted upfield significantly such that it is between the signals of 3-H and 3′-H. When $\mathbf{365_A}$ and $\mathbf{366_b}$ are reacted at room temperature, product $\mathbf{367_{Ab}}$ is obtained in 80% yield. However, the product of the reaction between $\mathbf{365_B}$ and $\mathbf{366_b}$, which is also white crystals, gives an IR spectrum very different from that of $\mathbf{367_{Ab}}$. In addition to the typical β-lactam carbonyl absorption at 1700 cm^{-1}, another band at 1640 cm^{-1} is also observed. The mass spectrum



Synthesis of 2,3-dihydro-1,5-benzothiazepines **326** promoted by SmI_2

326	X	R^1	R^2	Time (h)	Yield (%)[(a)]
(a)	H	C_6H_5	Ph	4	86
(b)	Cl	C_6H_5	Ph	4	83
(c)	Cl	*p*-ClC_6H_4	Ph	3	78
(d)	Cl	*p*-$CH_3C_6H_4$	Ph	4	80
(e)	Cl	*p*-$CH_3C_6H_4$	Ph	4	77
(f)	Cl	3,4-$(OCH_2O)C_6H_3$	Ph	4	85
(g)	Cl	C_6H_5	Ph CH=CH	8	52
(h)	H	C_6H_5	CH_3	10	43

[(a)] Yields of crude product based on bis (*o*-nitrophenyl)disulfides

Scheme 59: Ring-closure reactions between α,β-unsaturated ketones and the intermediate samarium diiodide (Kagan Reagent).

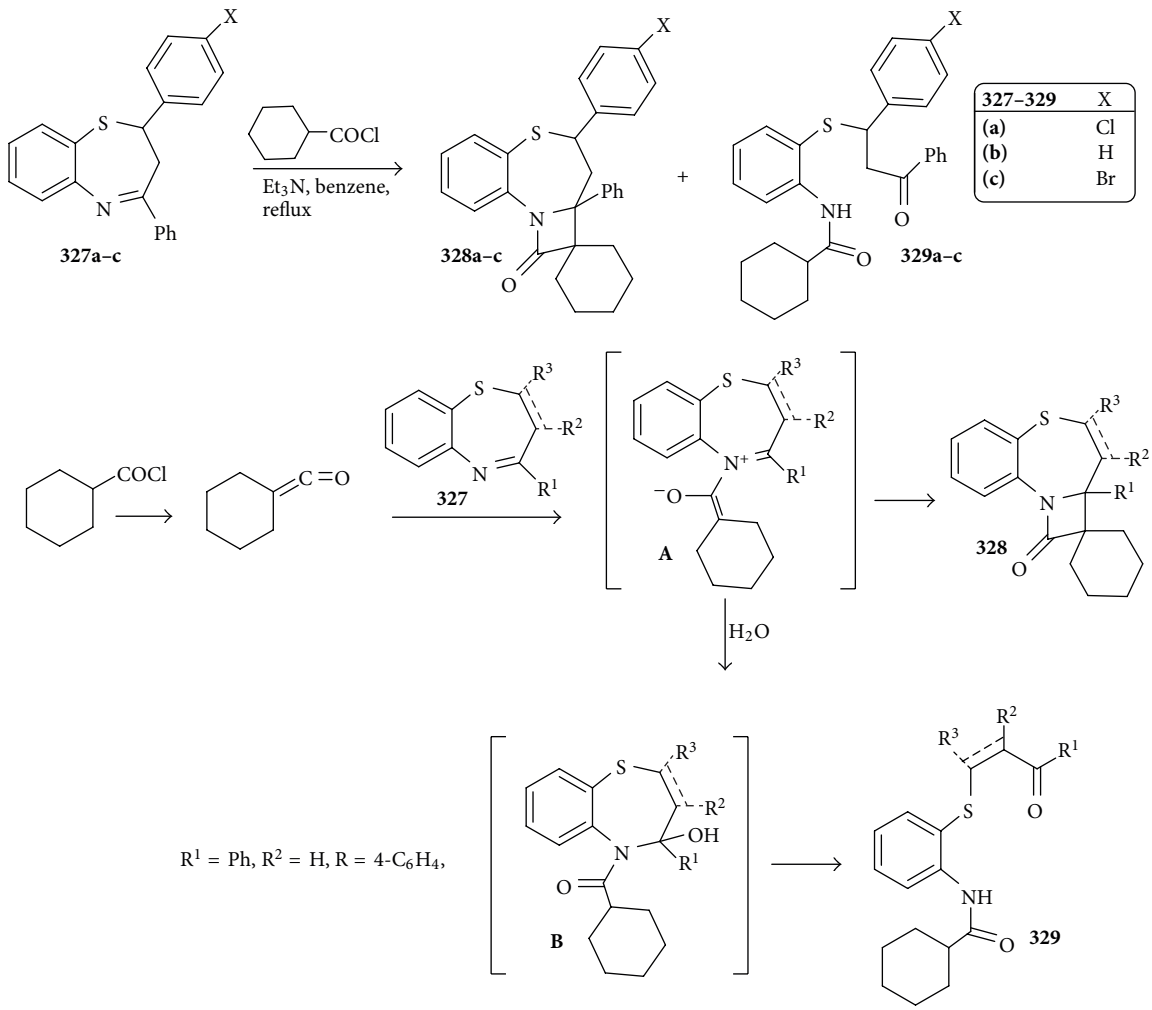
shows that four chlorine atoms are present in the molecule. It was therefore concluded that this is a product resulting from one molecule of $\mathbf{365_B}$ reacting with two molecules of $\mathbf{366_b}$. The NMR spectrum of this compound does not show an AMX signal attributable to the three protons on the seven membered ring but instead gives a signal corresponding to a 2H doublet with a coupling constant of 7 Hz at δ l.46. Other signals are: δ 3.98 (s, 3H), 4.85 (m, 1H), 4.20 (s, 1H), and 6.04 (d, 1H, J = 7. 1 Hz). Combining the NMR data with MS fragment analysis, it is reasonable to conclude that the seven-membered ring at $\mathbf{365_B}$ fragments during the reaction to give a product with structure $\mathbf{369_{Bb}}$. This shows that compounds $\mathbf{366_a}$ and $\mathbf{366_b}$ have different reactivity.

This reaction gives very different results at different temperatures. When carried out at room temperature, compounds $\mathbf{365_A}$ and $\mathbf{366_b}$ produced $\mathbf{367_{Ab}}$ as the major product. When carried out at reflux temperature, a compound bearing the structural features of $\mathbf{369_{Ab}}$ is obtained as the major product. The NMR spectrum of this $\mathbf{369_{Ab}}$ shows two doublets at δ 6.44 and 6.96 (J = 16 Hz), suggesting that the two protons of the –CH=CH– double bond in $\mathbf{369_{Ab}}$ are *trans* to each other, while in the case of $\mathbf{369_{Bb}}$, these two protons are *cis* to each other.

When the reaction of $\mathbf{365_A}$ and $\mathbf{366_a}$ was carried out at reflux temperature, a low melting-point crystalline solid was obtained in addition to a small amount of the expected $\mathbf{367_{Aa}}$. The IR spectrum of this compound showed absorption at 1676 cm^{-1}; while the band at 1750 cm^{-1}, which is the typical carbonyl absorption for a β-lactam, is not present. Mass spectrometry shows that this compound has a molecular ion peak with the same m/z value as $\mathbf{367_{Aa}}$, but that the fragmentation pattern is different. This suggests that this newly obtained compound is a structural isomer of $\mathbf{367_{Aa}}$. The NMR spectrum of this compound did not show signals for the three protons of the AMX system but showed two doublets at δ 3.50 and 3.95 with a coupling constant of J = 13.5 Hz, and two doublets at δ 6.53 and 6.88 ppm with a coupling constant of J = 15.7 Hz. This indicates that this compound should have the structure of $\mathbf{368_{Aa}}$, with the two protons on the C=C double bond in a *trans* relation. When $\mathbf{365_B}$ and $\mathbf{366_a}$ were heated under reflux, the low melting-point compound $\mathbf{368_{Ba}}$ was obtained along with a small amount of the expected compound $\mathbf{369_{Ba}}$. The IR spectrum of $\mathbf{368_{Ba}}$ showed an absorption at 1680 cm^{-1}. Its mass spectrum shows an M^+ ion with m/z 359, but with a different fragmentation pattern from that of $\mathbf{367_{Ba}}$. The NMR spectrum of compound $\mathbf{368_{Ba}}$ showed two groups of signals: δ 1.46 (d, 3H, J = 4.8), 3.77 (s, 3H), 4.02 (dd, 2H, J = 13), 4.52 (m, 1H), 5.99 (d, 1H, J = 6.4); 1.48 (d, 3H, J = 4.8), 3.82 (s, 3H), 4.12 (s, 2H), 4.71 (m, 1H), 6.19 (d, 1H, J = 7.1), and 6.85–7.51 (m, 16H) for aromatic protons. The chemical shifts for the major signals of these two compounds are quite similar, with about 0.2 ppm differences. This may indicate that $\mathbf{368_{Ba}}$ is a mixture of a pair of stereoisomers.

As with the case of $\mathbf{368_{Ba}}$, the NMR spectrum of the reaction product of $\mathbf{365_B}$ with $\mathbf{366_b}$ showed two groups of NMR signals, one of which is described as: δ 1.48 (d, 3H, J = 6.9), 3.80 (s, 3H), 4.54 (m, 1H), 5.99 (d, 1H, J = 7.3), 6.27 (s, 1H); while the other is as follows: δ 1.55 (d, 3H, J = 6.4), 3.82 (s, 3H), 4.79 (m, 1H), 6.24 (s, 1H), 6.27 (d, 1H, J = 7.3). Signals for aromatic protons appear at δ 6.87–7.48 (m, 16H). This suggests that these two compounds may be diastereomers of $\mathbf{368_{Ba}}$. Based on these observations, there is a propose reaction mechanism.

If the reaction proceeds as proposed, there should be an intermediate **371**, and a rearrangement should occur with the presence of a nucleophile in the reaction system. When trace amount of water was added to the above reaction system,



Proposed reaction progress of benzoheteroazepines with cyclo hexanecarboxylic chloride in the presence of triethylamine.

Scheme 60: Staudinger reaction of 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepines with cyclohexane carboxylic chloride in the presence of triethylamine in anhydrous benzene.

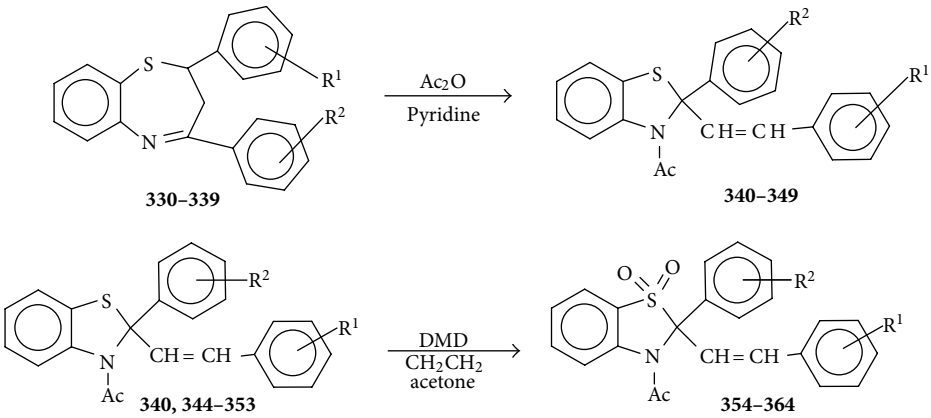
a different result was obtained. The product with structure **370** was isolated, indicating the possible existence of intermediate **371** [79] (Scheme 62).

5.4. Synthesis of Dihydro1,5-benzothiazepines via Reactions of α,β-Unsaturated Ketones with o-Aminothiophenol. Dihydrobenzothiazepines,1,5-benzothiazepines **372** (prepared from *o*-aminothiophenol and *α,β*-unsaturated ketones in excellent yields) were reacted with various acyl chlorides, including phthalimidoacetyl chloride (prepared from phthalic anhydride and glycine), chloroacetyl chloride, dichloroacetyl chloride, and phenoxyacetyl chloride, in the presence of Et_3N in anhydrous benzene, to give 2a,4-disubstituted 2-phthalimido,2-chloro-,2,2-dichloro-, or 2-phenoxy-2,2a,3,4-tetrahydro-1*H*-azeto[2, 1-*d*][1, 5]benzothiazepine-1-ones **373–376** through parallel solution-phase synthesis. (Yield of some representative examples: **373a**: 79%, **374i**: 67%, **374k**: 60%; **375b**: 86%, **375d**: 73%).

This could be rationalized as follows. A zwitterionic intermediate **377** could be formed from two pathways: (i) Triethylamine abstracts an *α*-hydrogen next to the carbonyl group in the positively charged *N*-acylated benzothiazepine intermediate which in turn yields the less sterically hindered zwitterionic intermediate **377**. (ii) The heterocyclic nitrogen atom of the benzothiazepine scaffold **1** forms an N–C bond with the carbonyl group of a ketene, the latter generated from acyl chloride and triethylamine. The N–C interaction should occur from the less hindered side of the ketene over the small group H for phthalimidoketene, chloroketene, and phenoxyketene.

The zwitterionic intermediate **377** then undergoes conrotatory ring closure to form a *β*-lactam ring to afford azeto[2, 1-*d*][1, 5]benzothiazepin-1-ones **373–376**.

Because ring closure in the downward direction of the N–C bond in the thiazepine ring (path a) would require ring constriction of the thiazepine ring, this path is not energetically favorable. Although the conrotatory ring closure could occur



	R^1	R^2		R^1	R^2
330,340	4-*i*Pr	2-OAc	**335,345**	4-Cl	2-OAc
331,341	2-OMe	2-OAc	**336,346**	2,4-Cl_2	2-OAc
332,342	3,4,5-$(OMe)_3$	2-OAc	**337,347**	3,4-Cl_2	2-OAc
333,343	2-Cl	2-OAc	**338,348**	4-Cl	2-OAc
334,344	3-Cl	2-OAc	**339,349**	2,4-Cl_2	4-Me

350,354: R^1=R^2 = H
351,355: R^1=H, R^2 = 2-OAc
352,356: R^1= H, R^2 = 4-OAc
353,357: R^1=H, R^2 = 4-OMe
340,358: R^1= 4 -*i*Pr, R^2 = 2-OAc
344,359: R^1= 3 -Cl, R^2 = 2-OAc

345,360: R^1 = 4 -Cl, R^2 = 2-OAc
346,361: R^1 = 2,4 -Cl_2, R^2 = 2-OAc
347,362: R^1 = 3,4 -Cl_2, R^2 = 2-OAc
348,363: R^1 = 4 -Cl, R^2 = 4-OAc
349,364: R^1 = 2,4 -Cl_2, R^2 = 4-Me

Scheme 61: Ring contraction 1,5-Benzothiazepins.

in the upward direction of the N–C bond (path b) to provide products with *cis* R^1, R^2, and R^3 substituents, this process is forbidden because R^1 and R^2 substituents occupy in the steric hindered 1,3-quasi-axial positions of the thiazepine ring.

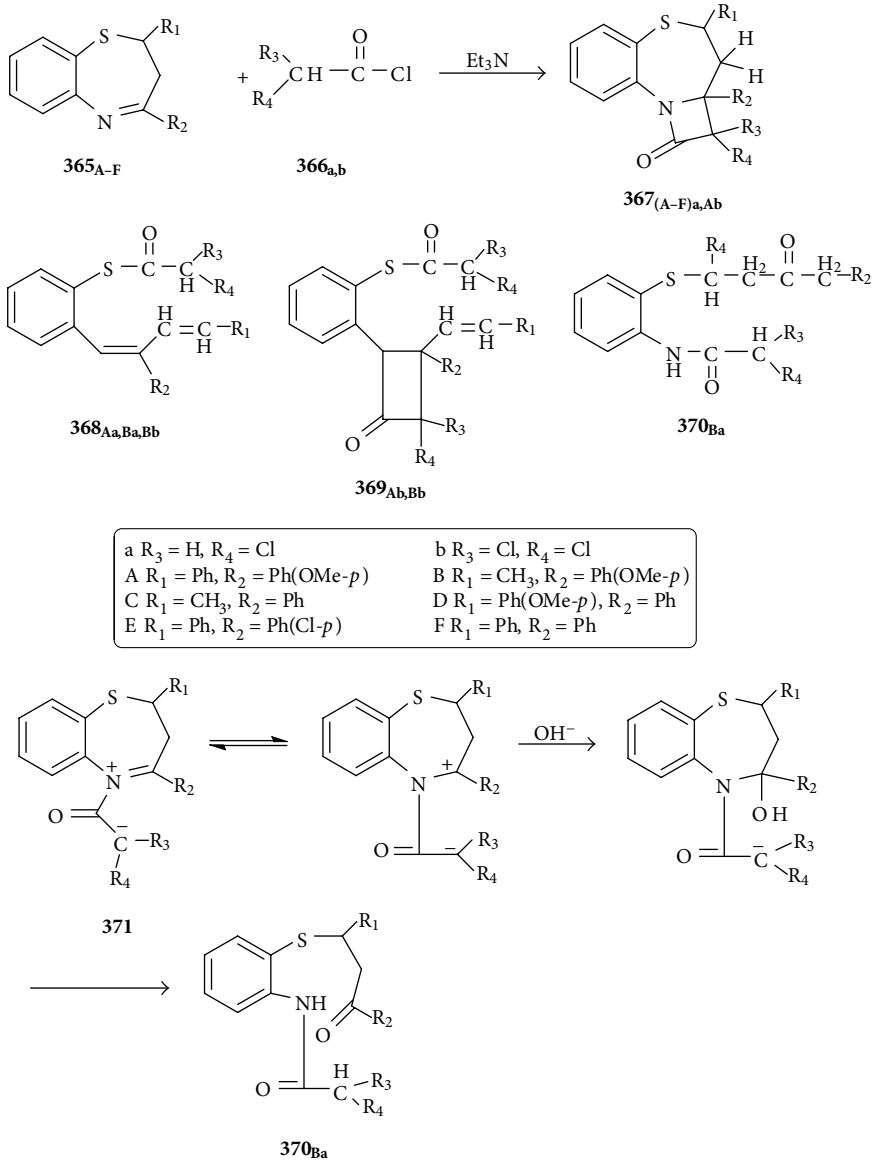
The conrotatory ring closure can occur only with the sense shown (downward, path c), in which the thiazepine framework rotates downwards to yield a boat-like product *via* β-lactam ring formation. If the conrotatory ring closure, in which the whole thiazepine ring rotates upwards (path d), occurs upwards, a β-lactam ring would form from the inside of the thiazepine ring. This is an unfavorable process because the lope of the orbital in the thiazepine locates in the inside of the boat bottom; it cannot overlap with the lope of the orbital in the enolate part.

This boat-like product formed then undergoes conformation transfer to produce finally the predominant chair-like products **373–376**. Thus, only one pair of diastereomers of each of cycloadducts, with shown relative stereoconfiguration, was obtained in the cycloaddition reaction. Namely, the cycloaddition is a stereospecific reaction in which R^2 and R^3 (phthalimido, chloro, *or* phenoxy group) in the products **373**, **374**, and **376** are *cis* configuration [80] (Scheme 63).

5.5. Reduction of Oxygen-Bridged 1,5-Benzothiazepines. The 2,3,4,5-tetrahydro-1,5-benzothiazepine derivatives **39a** (Scheme 6) and **b** upon reduction with $LiAlH_4$ (3M) yielded **378a** and **b** (39 and 45% yield, resp.). Although the reduction of both double bonds to give **379a** and **b** is expected, only the C=N double bond was reduced and the oxygen bridge was opened as well to give **378a** and **b**. In an attempt to achieve a fully reduced 2,3,4,5-tetrahydro-1,5-benzothiazepine derivative, a higher amount of $LiAlH_4$ was used for the reduction of **39b** as an example, and the reaction mixture was refluxed for 30 minutes after stirring overnight at room temperature. Thereby, a new reduction benzothiazepine product **380** was isolated (65% yield) [9] (Scheme 64).

5.6. Ring-Opening Reaction of 3-(1H-1,2,4-Triazol-1-yl)-1,5-benzothiazepine with Phenylonitrile Oxide. Benzohydroximinoyl chloride when added while stirring to a solution of 1,5-benzothiazepine containing 1,2,4-triazole moiety **43** dissolved in methylene chloride while drop wise adding of triethylamine gave the ring-opened product (*Z*)-2-((*Z*)-((*Z*)-1,3-diphenyl-2-(1*H*-1,2,4-triazol-1-yl)allylidene)-amino)phenyl-*N*-hydroxybenzimidothioate **381** (27.3% yield) and not the expected 1,5-thiazepine **382** [10] (Scheme 65).

5.7. Reaction of 2,3-Dihydro[1,5]benzothiazepines with Benzohydroximinoyl Chloride. When selected benzohydroximinoyl chloride derivatives were added to a stirred solution of the 1,5-benzothiazepine **45a–d** in methylene chloride, Et_3N dissolved in dichloromethane, and the reaction mixture



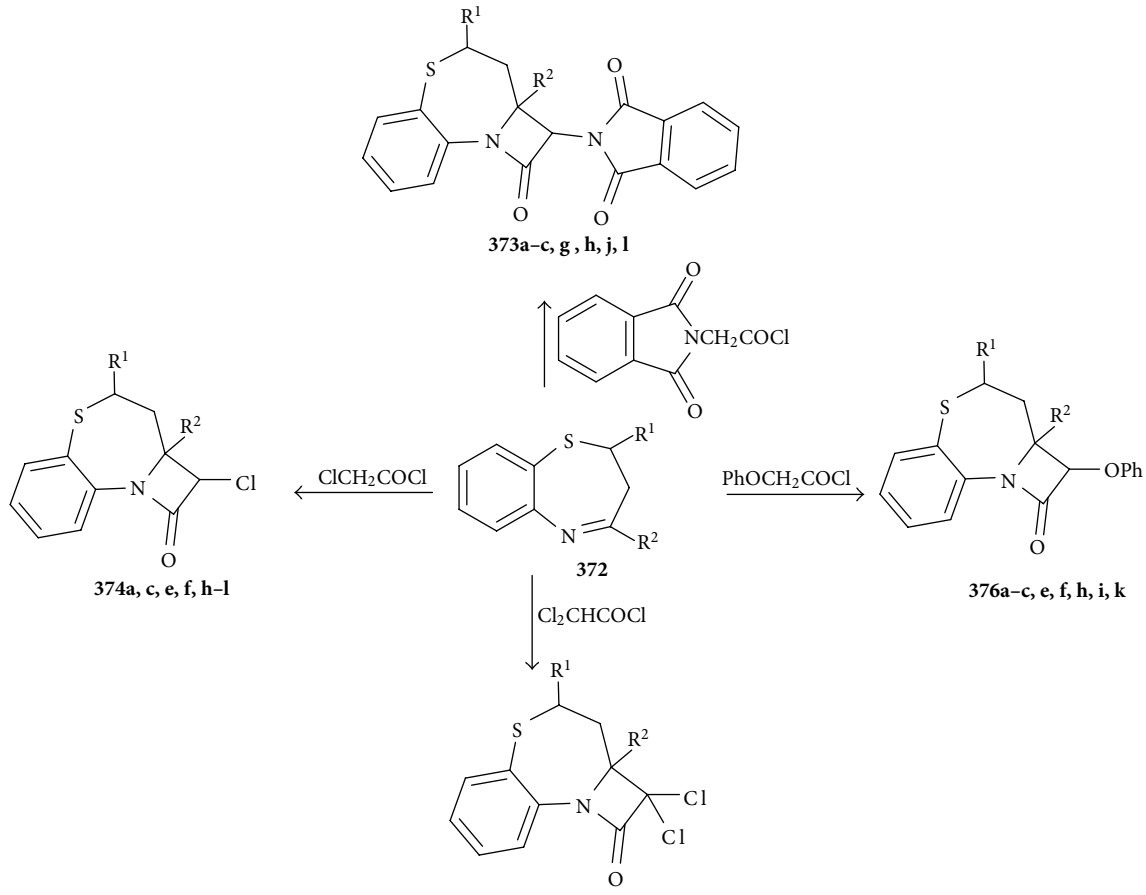
Scheme 62: Reactions between 2,4-disubstituted-2,3-dihydro-1,5-benzothiazepines and ketenes.

stirred at room temperature for 4 days, the oxadiazole-thiazepine **383a–l** were obtained in moderate yield (31–48%) [11] (Scheme 66).

5.8. Reaction of 1.5-Benzothiazepines with Chloroacetyl Chloride and Phenoxy-acetyl Chloride in Presence of Et_3N. The 1,5-benzothiazepines **49a–e** when reacted with chloroacetyl chloride *or* phenoxyacetylchloride, in the presence of triethylamine in anhydrous benzene, gave 2-chloro- or 2-phenoxy-2a-(2-phenyl-1,2,3-triazole-4-yl)-4-aryl-2,2a, 3,4-tetrahydro-1*H*-azeto[2, 1-*d*][1, 5]benzothiazepin-1-ones **384a–j** in 59–36% yield through parallel solution-phase synthesis [12] (Scheme 67).

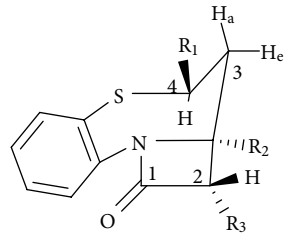
5.9. 1,3-Dipolar Cycloadditions of (E)-2-(7-Phenoxyquinolin-6-yl)-4-p-substituted Phenyl-2,3-dihydrobenzo[1,5]thiazepine with Benzohydroximinoyl Chlorides or Hydrazonoyl Chlorides in the Presence of Et_3N. The benzothiazepine derivatives **57a–c** underwent 1,3-dipolar cycloadditions with benzohydroximinoyl chlorides or hydrazonoyl chlorides in the presence of Et_3N to afford the formation of cycloadducts **385a–l** and **386a–i**, respectively.

A conceivable intramolecular 1,3-dipolar cycloaddition mechanism is proposed. The conformation of the central 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepine ring adopts a boat-like conformation. In the presence of Et_3N, the nitrile oxide generated *in situ,* C=N double bond in the benzothiazepine ring forms a cyclic transition state, the σ-bonds of C–N and C–O were formed simultaneously to obtain the 1,2,4-oxadiazole ring, the central thiazepine ring of the cycloadduct also adopts a boat-like conformation. The plausible mechanism of compounds **386a–I** was proposed analogously [14] (Scheme 68).



Parallel solution-phase synthesis of **2a**,3,4,5-tetrahydro-1*H*-azeto[2,1 *d*][1,5]benzothiazepin-1-ones in the presence of NEt_3

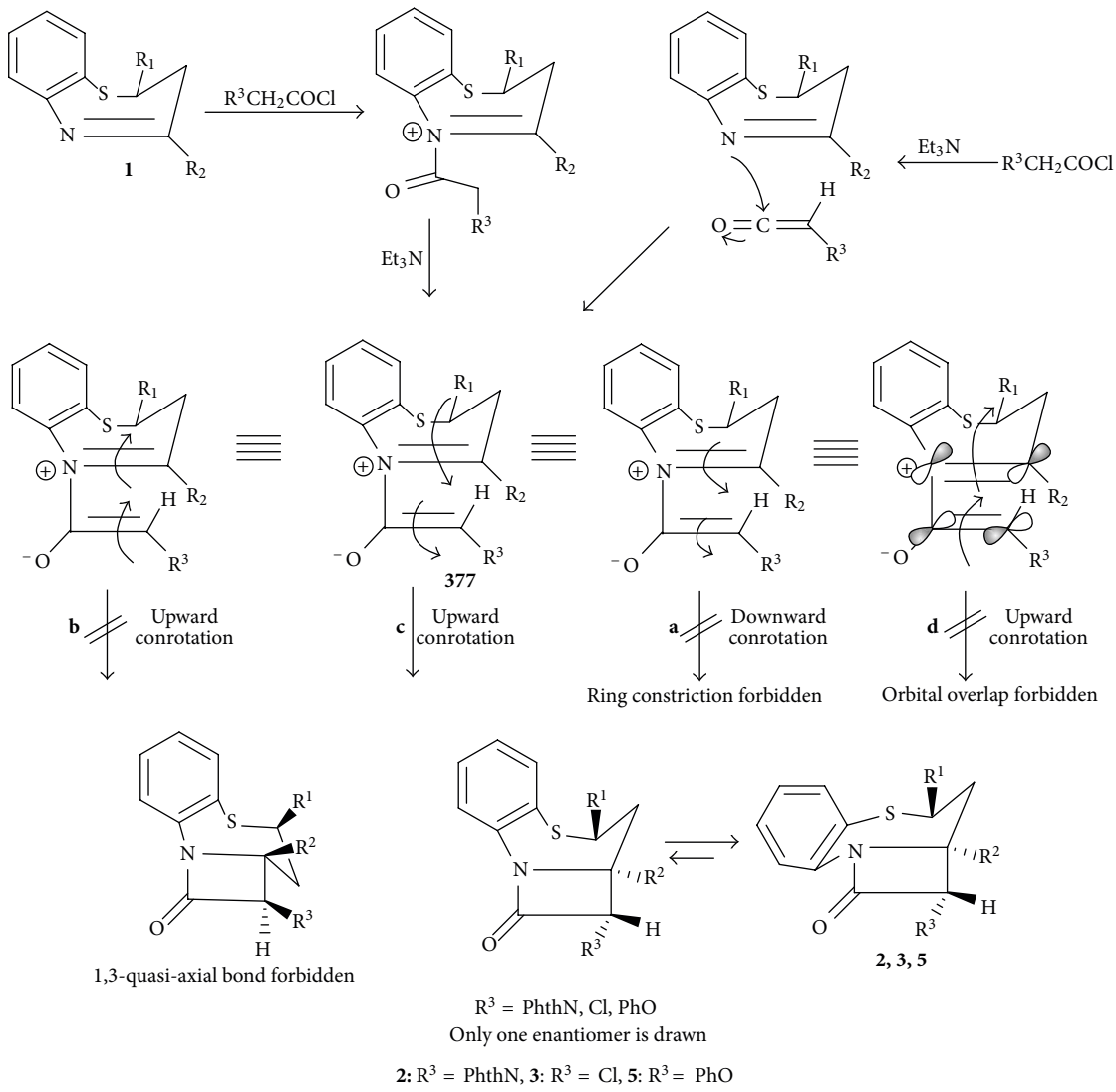
	(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(i)	(j)	(k)	(l)
R^1	Me	Me	Me	Me	Ph	2-ClPh	3-ClPh	4-ClPh	4-BrPh	4-MeOPh	Ph	Ph
R^2	Ph	4-MePh	4-MeOPh	4-FPh	Ph	Ph	Ph	Ph	Ph	Ph	4-ClPh	4-MeOPh



373, 374, 376

Stereostructure of 2,2a,4-trisubstituted 2a,3,4,5-tetrahydro-1H-azeto[2,1-d][1,5]benzothiazepin-1-ones.

Scheme 63: Continued.

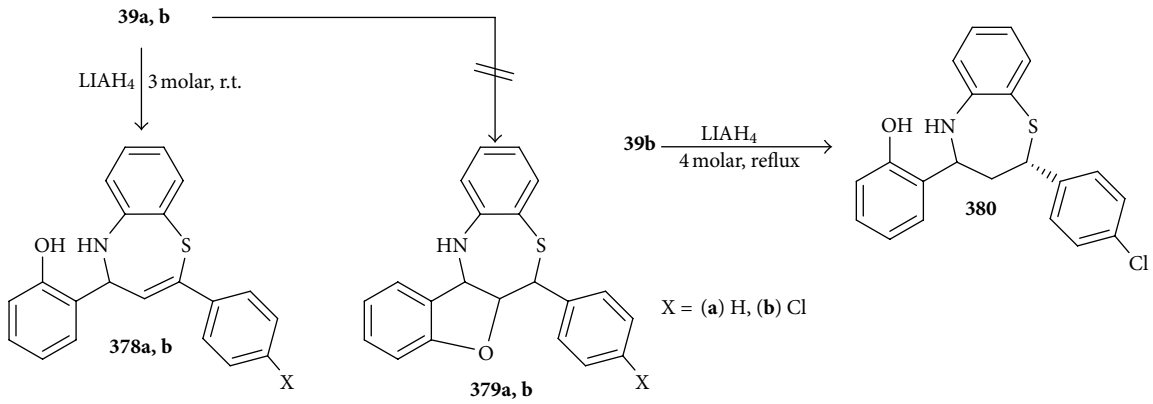


Stereochemistry in the reaction process of 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepines and acyl chlorides in the presences of triethylamine

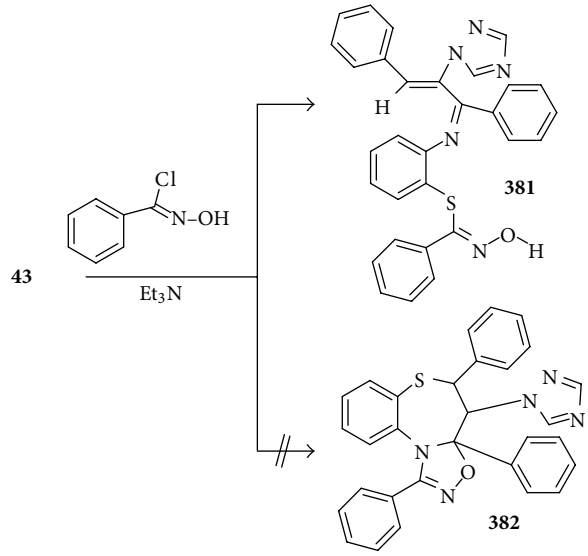
Scheme 63: Synthesis of dihydro-1,5-benzothiazepines *via* reactions of α,β-unsaturated ketones with *o*-aminothiophenol.

5.10. 1,3-Dipolar Cycloaddition of Nitrile Oxide and Triethylamine, with the Hexa Hydropyrido-[3,4-c][1,5]benzothiazepines. The 1,3-dipolar cycloaddition of nitrile oxide, generated *in situ* from benzohydroximinoyl chloride and Et_3N, with 2-methyl-11-aryl-4-[(*E*)-arylmethylidene]-1,2,3,4, 11,11-a hexahydropyrido[3, 4-*c*][1, 5]benzothiazepines **103a–j** afforded novel 6-methyl-1-phenyl-8-aryl-4-[(*E*)-arylmethylidene]-4,5,6,7,7a,8-hexahydro[1, 2, 4]oxadiazolo[5, 4-d]pyrido[3, 4-*c*]-[1, 5]benzothiazepines **387a–j**. This reaction completed in 20–30 min affording the benzothiazepine **387** almost quantitatively. The triethylamine hydrochloride formed during the reaction can be filtered, neutralized and reused. Hence the only waste generated in this reaction is hydrochloric acid and the atom economy of the reaction is very high, that is, 94%. Therefore, this study presented a highly atom economic protocol for the stereoselective synthesis of a series of new [1, 2, 4]oxadiazolo[5, 4-*d*]pyrido[3, 4-*c*][1, 5]benzothiazepines *via* nitrile oxide cycloaddition [27] (Scheme 69).

5.11. Reduction of Dihydrobenzothiazepine with Either $NaBH_4$ or with o-ATP or DAPDS and with H_2 Using Pt. Sodium borohydride reduction of the dihydrobenzothiazepine **156b** provided the tetrahydrobenzothiazepine **388**. Compound **388** is also formed by the reduction of **156b** with *o*-ATP (Adenosine-5′-triphosphate) (catalytic amount) in ethanol containing an acid. However, it is well known that *o*-ATP is contaminated with a little amount of di *o*-aminophenyl disulphide (DAPDS) (**VI**) due to its aerial oxidation. Hence, the involvement of DAPDS in the reduction of **156b** could not be ruled out. Keeping this in view, **156b** was also treated with DAPDS as well as *o*-ATP in refluxing EtOH in the presence of an acid (HCl or HBr). In all of these cases



Scheme 64: Reduction of oxygen-bridged 1,5-benzothiazepines.



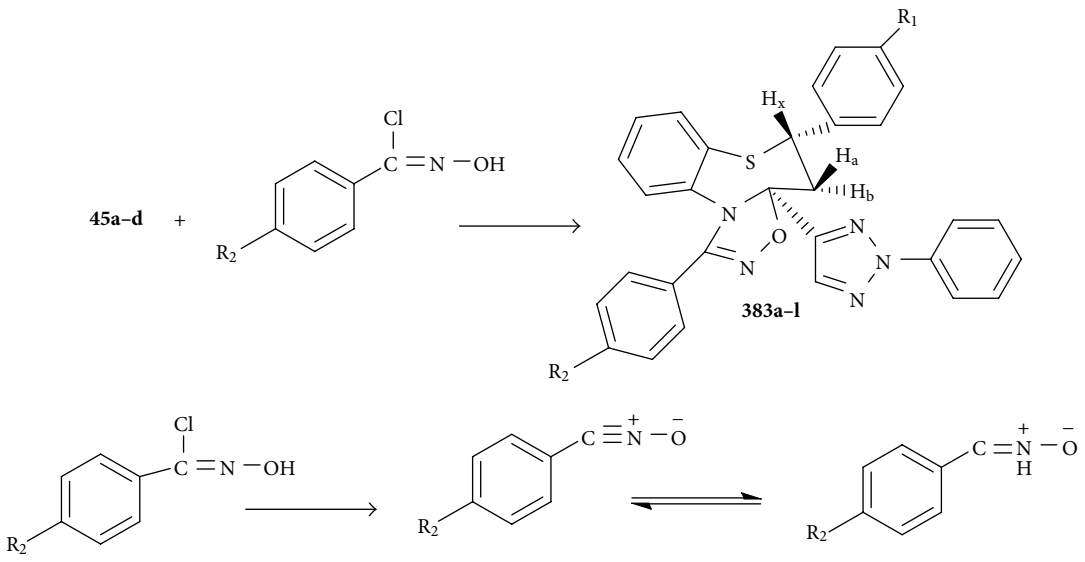
Synthesis of (*Z*)-2-((*Z*)-((*Z*)-1,3-diphenyl-2-(1*H*-1,2,4-triazol-1-yl)allylidene)amino) phenyl-*N*-hydroxybenzimidothioate **381**

Scheme 65: Ring-opening reaction of 3-(1*H*-1,2,4-triazol-1-yl)-1,5-benzothiazepine with phenylonitrile oxide.

388 was obtained in good yields (75%). Because reduction is catalyzed by both *o*-ATP as well as DAPDS it may be suggested that in the reduction of **156b** with *o*-ATP/H^+ in EtOH, the effective catalyst is *o*-ATP. The nucleophilic addition of *o*-ATP to the initially formed carbocation **389** may result in the formation of **390**, which may cleave to **388** and 1,2-benzothioquinone imine **391**. The addition of EtOH to **391** may give rise to another intermediate **392**, which may in turn regenerate *o*-ATP with a concomitant elimination of the corresponding carbonyl compound. Compound **391** may re-enter the reductive cycle, which may continue until **156b** is completely reduced to **388**. However, when DAPDS is used in place of *o*-ATP, it may first undergo acid-catalyzed dis-proportionation to give **391** and *o*-ATP, which may catalyze the reduction as previously described.

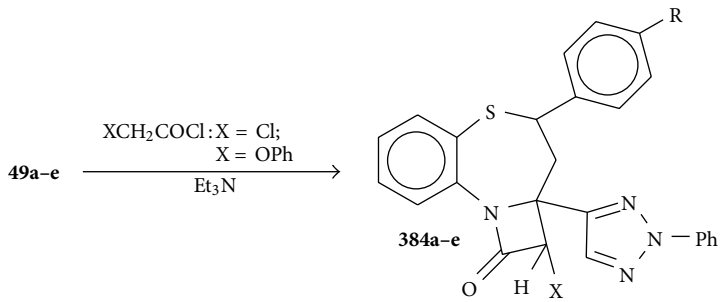
It is worth mentioning that the present reductive one-step conversion of **156b** into **388** by using *o*-ATP or DAPDS in acidic EtOH is quite significant as it constitutes a convenient access to tetrahydrobenzothiazepine derivatives **388**. Also this procedure is cheaper than the reduction of **156** to **388** by using $NaBH_4$ as a reducing agent.

The reduction of **157a** with H_2 using Pt resulted in the formation of tetrahydrobenzothiazepine derivative **388**. The reduction product **388** obtained by this method was found identical to the product that was obtained by the reduction of **156** with either $NaBH_4$, *o*-ATP, or DPDS in EtOH containing



383	R_1	R_2	Yield (%)	383	R_1	R_2	Yield (%)
(a)	H	H	35	**(g)**	Cl	H	39
(b)	H	OMe	31	**(h)**	Cl	OMe	48
(c)	H	Cl	36	**(i)**	Cl	Cl	43
(d)	OMe	H	43	**(j)**	NO_2	H	36
(e)	OMe	OMe	46	**(k)**	NO_2	OMe	37
(f)	OMe	Cl	44	**(l)**	NO_2	Cl	32

Scheme 66: Reaction of 2,3-dihydro[1, 5]benzothiazepines with benzohydroximinoyl chloride.



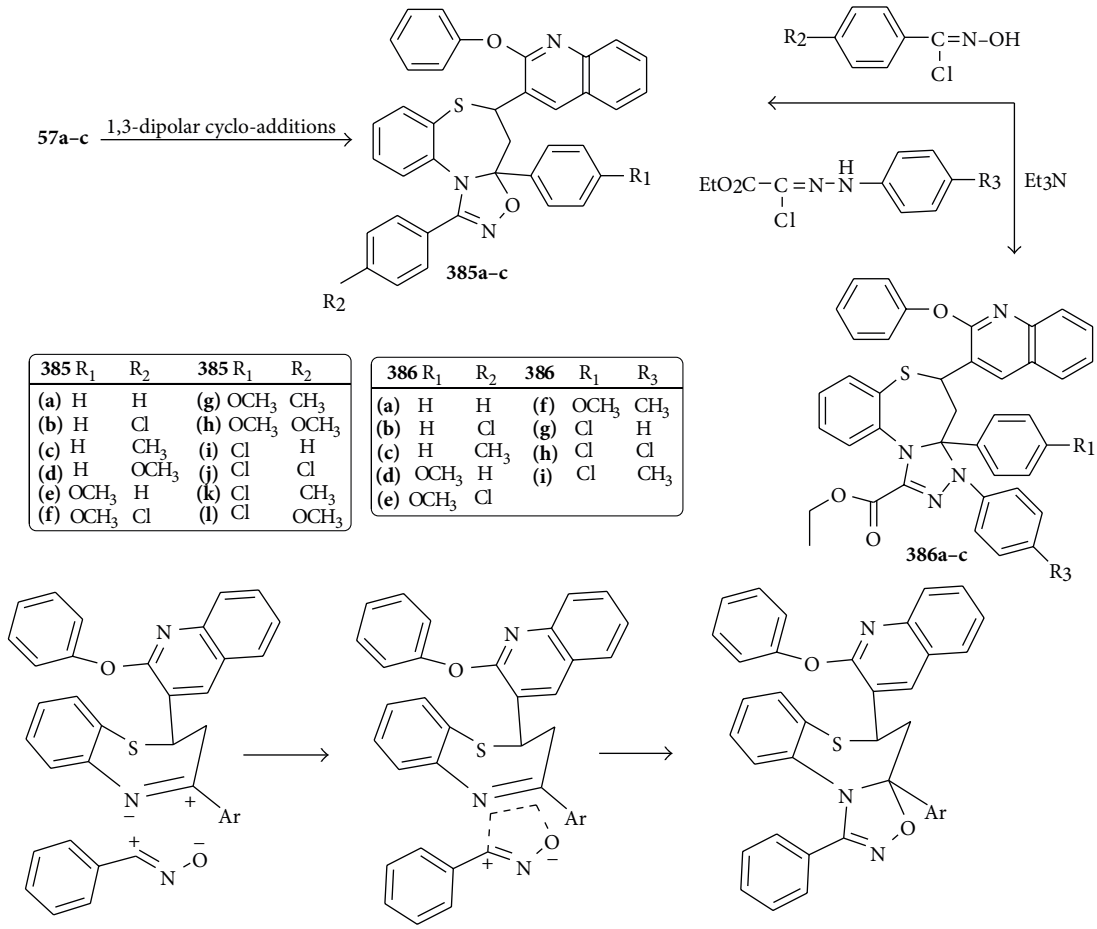
384: (**a**) R = H, X = Cl, (**b**) R = CH_3, X = Cl, (**c**) R = OCH_3, X = Cl, (**d**) R = Cl, X = Cl, (**e**) R = NO_2, X = Cl, (**f**) R = H, X = OPh, (**g**) R = CH_3, X = OPh, (**h**) R = OCH_3, X = OPh, (**i**) R = Cl, X = OPh, (**j**) R = NO_2, X = OPh

Scheme 67

an acid. This was further confirmed by TLC, m.p., and mixed m.p.s of these compounds. The formation of **388** was further confirmed by the conversion into the corresponding acetyl derivatives **393** using Ac_2O and pyridine [37] (Scheme 70).

5.12. Extrusion of Sulfur Atom of the Benzothiazepine. The benzothiazepine structures **182** seemed to be quite unstable and, under basic conditions or on heating, can be transformed into quinoline rings **394** by elimination of the sulfur atom. Therefore, upon heating the benzothiazepine **182a** to 120°C, an efficient extrusion of sulfur atom for the benzothiazepine with the aromatic substituent was observed and gave 3-fluoro-2-(4-fluorophenyl)-4-(perfluorobutyl)quinoline **394a** in 80% yield [44–47] (Scheme 71).

5.13. Reactions of 2-Carboxy-2,3-dihydro-1,5-benzothiazepines with K_2CO_3 and Chloroacetyl Chloride under Microwave Irradiation. The substituted-1,5-benzothiazepine **202a** was adsorbed on activated potassium carbonate with the help of methanol. The solvent was removed under reduce pressure using a rotatory evaporator. To this, chloroacetyl chloride was added and mixed thoroughly and resulting reaction mixture was irradiated in the microwave oven. After completion of the reaction (monitored by TLC), the reaction



Proposed intramolecular 1,3-dipolar cycloaddition mechanism of cycloadduct **385a**

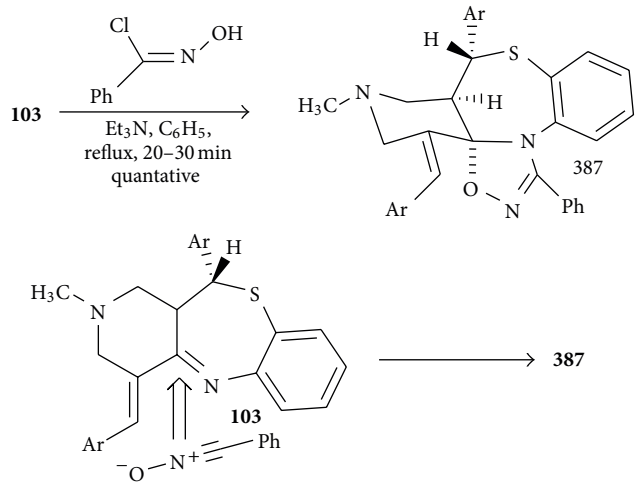
Scheme 68: 1,3-Dipolar cycloadditions of (*E*)-2-(7-phenoxyquinolin-6-yl)-4-*p*-substituted phenyl-2,3-dihydrobenzo[1, 5]thiazepine with benzohydroximinoyl chlorides or hydrazonoyl chlorides in the presence of Et_3N.

mixture was cooled (r.t.), added to ice water and the supernatant aqueous layer decanted and filtered to yield desired azeto[2, 1-*d*][1, 5]benzothiazepine **395a**. Yield = 78%; time = 4 min. All other azeto-[2, 1-*d*][1, 5]benzothiazepine **395b–m** were similarly prepared under solvent-free conditions using K_2CO_3 under microwaves [53] (Scheme 72).

5.14. Hydrolysis of Sodium Salts of 1,5-Benzothiazepine-2-carboxylic Acid. The sodium salts of 1,5-benzothiazepine-2-carboxylic acid **396a–b** were obtained by hydrolysis of **238a–b** in water solution [59] (Scheme 73).

6. Infrared, Ultraviolet, ^{1}H, ^{13}C NMR, and ^{19}F (Selected Examples)

6.1. Infrared. Fourier transfer infrared (KBr) of 2-(2-phenoxyquinolin-3-yl)-4-phenyl-2,3-dihydrobenzo[1, 5]thiazepine **57a** (Scheme 74) and 5-(2-phenoxyquinolin-3-yl)-1, 3a-diphenyl-4,5-dihydro-3a*H*-benzo[1, 2, 4]oxadiazolo[4, 5-*d*][1, 5]thiazepine **385a** contained absorption bands for C=N, and C–O–C around 1596 and 1244 cm^{-1} regions, respectively [14]. The spectrum of (*E*)-2-(2-(4-(phenylthio) phenyl)-2,3-dihydrobenzo[1, 5]thiazepin-4-yl) phenol **70a** showed bands for OH, C=C, C=N and C–S–C at 3430, 1622, 1460, and 673 cm^{-1} [3]. The appearance of a sharp absorption band near 1620 cm^{-1} confirmed the presence of C=N group in the spectrum of (*S*, *E*)-2-(benzo[*d*][1, 3]dioxol-5-yl)-4-phenyl-2,3-dihydrobenzo[1, 5]thiazepine **94a** [25]. 2-chloro-7-methoxy-1-oxo-2a-phenyl-2,2a,3,4-tetrahydro-1*H*-azeto[1, 2-*d*]benzo[1, 5]thiazepine-4-carboxylic acid **99a** revealed in its IR spectrum two carbonyl bands at 1680 and 1725 cm^{-1}, beside a broad band for OH group around 3288 cm^{-1} and another band at 748 cm^{-1} which could be due to C–Cl oscillating frequencies [26]. The IR spectrum (KBr) of 2-(2-chlorophenyl)-8-ethoxy-4-(thiophen-2-yl)-2,3, 4,5 tetrahydrobenzo[1, 5]thiazepine **241l** cleared the presence of NH (br,3146) and C=O (1690–1650) cm^{-1} [60]. IR spectrum (KBr) of 2-(4-methyl-1-oxo-2a-phenyl-2,2a,3,4-tetrahydro-1*H*-azeto[1, 2-*d*]benzo[1, 5]thiazepin-2-yl)isoindoline-1,3-dione **373a** showed three carbonyl absorption bands around 1761, 1719, and 1641 cm^{-1} regions. Meanwhile, the IR spectra of the azeto derivatives 4-(4-bromophenyl)-2-chloro-2a-phenyl-2,2a,3,4-tetrahydro-1*H*-azeto[1, 2-*d*]benzo[1, 5]thiazepin-1-one **474i** and



Diastereofacial selective cycloaddition of nitrile oxide to **103**.

Synthesis of [1, 5] benzothiazepines **103** and **387**

Ar **103** or **387**	**103**	MW method		Conventional method		**387**	Yield[(b)] (%)
		Time (min)	Yield[(a)] (%)	Time (min)	Yield (%)		
(a) Ph		6	80	10	30	**(a)**	94
(b) 4-Cl-Ph		8	79	10	28	**(b)**	96
(c) 4-Me-Ph		8	75	10	25	**(c)**	95
(d)4-MeO-Ph		8	70	10	21	**(d)**	98
(e) 4-F-Ph		10	70	11	23	**(e)**	95
(f) 3-F-Ph		4	80	10	27	**(f)**	96
(g) 2-Cl-Ph		6	72	10	25	**(g)**	95
(h) 2-MePh		8	75	11	24	**(h)**	96
(i) 2-Thienyl		6	80	11	26	**(i)**	94
(j) 1-Naphthyl		6	75	10	25	**(j)**	97

[(a)] Yield after recrystallisation. [(b)] Yield after column purification.

Scheme 69: 1,3-Dipolar cycloaddition of nitrile oxide and triethylamine, with the hexa hydropyrido-[3,4-c][1, 5]benzothiazepines.

4-methyl-2-phenoxy-2a-phenyl-2,2a,3,4-tetrahydro-1*H*-azeto[1, 2-*d*]benzo[1, 5]thiazepin-1-one **376a** realized one carbonyl absorption band around 1771 and 1763 cm^{-1}, respectively [80].

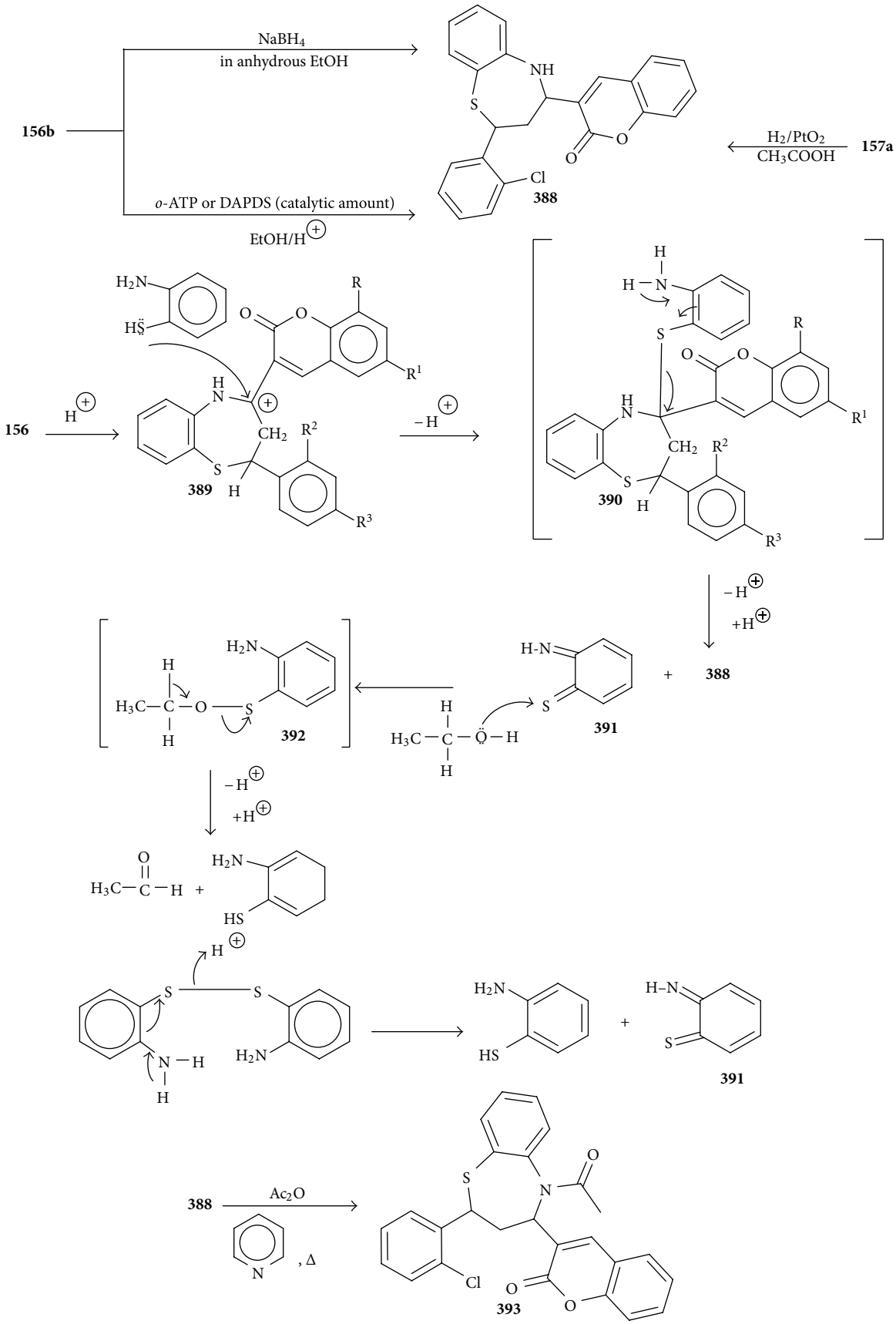
6.2. Ultraviolet. The ultraviolet spectra of several 1,5-thiazepine derivatives were characterized by electronic bands in 517–251 nm region, for example, **39a**: UV (MeOH), $\lambda_{max}(\varepsilon)$: 511 (56925), 323 (20780), 286 (21080), and 253 (31300) nm; **39b** and **d**: $\lambda_{max}(\varepsilon \times 10^{-3}$; MeOH): 511 (50.60), 328 (17.40), 287 (17.70), and 252 (24.50) and 517 (68.50), 353 (22.30), 297 (19.20), and 252 (32.20) nm, respectively [9]. In the UV/Vis spectra of 2,4-disubstituted benzo[*b*][1, 5]thiazepines **210**, three distinct absorption maxima are found at 254–276 nm, 280–329 nm, and 341–90 nm. In the case of the ferrocenyl-substituted derivative **210j** (Scheme 75), an additional longest wavelength absorption band is found at 486 nm arising from a metal-to-ligand charge transfer. Interestingly, all chromophores **210** are nonfluorescent upon excitation at 280–380 nm, for example, the UV/Vis (CH_2Cl_2) λ_{max} (ε) (nm) (mol^{-1} Lcm^{-1}) of **210j**: 262 (24600), 281 (26800), 380 (3500), and 486 (1500) [55].

6.3. ^{1}*H NMR.* Proton NMR spectrum (DMSO-d_6, 400 MHz) δ ppm: of (*Z*)-2-(4-fluorophenyl)-4-(2-(methylsulfonyl) phenyl)-3-(*o*-tolylsulfonyl)-2,3-dihydrobenzo[1, 5]thiazepine **36a** displayed signals at δ: 2.50 (s, 3H, Ar–CH), 3.27 (s, 3H, SO_2CH), 3.44–3.71 (two nondiagonistic doublets, 2H, 2 methine protons), and 6.82–8.13 (m, overlap, 16H, Ar–H) [8].

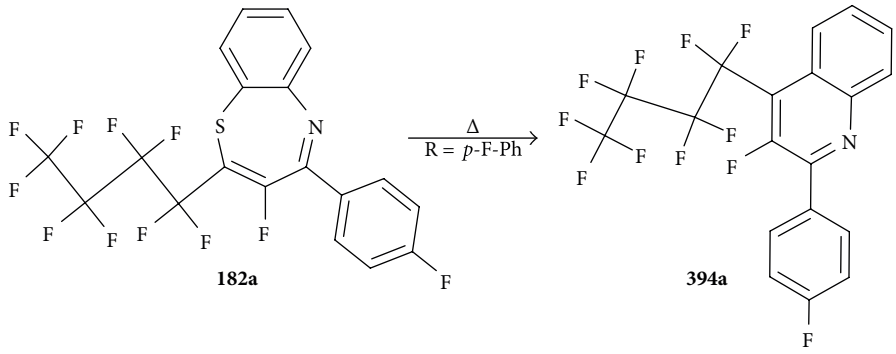
^{1}H-NMR (400 MHz, $CDCl_3$) of 1,5-diphenyl-3a-(2-phenyl-2*H*-1,2,3-triazol-4-yl)-4,5-dihydro-3a*H*-benzo[*b*][1, 2, 4]oxadiazolo[4, 5-*d*][1, 5]thiazepine **383a** showed signals at δ = 8.16 (s, 1H, triazole-H), 8.02–6.75 (m, 19H, Ar–H), 4.28–4.25 (dd, 1H, H_{-x}, J_{ax} = 5.26 H_z, J_{bx} = 12.01 Hz), 3.40–3.35 (dd, 1H, H_{-a}, J_{ax} = 5.26 H_z, J_{ab} = 16.00 H_z), and 3.28–3.25 (dd, 1H, H_{-b}, J_{bx} = 12.01 H_z, J_{ab} = 16.00 H_z) [11].

The PMR spectrum [300.13 MHz] [DMSO-d_6] of (*S*, *E*)-2-(benzo[*d*][1, 3]dioxol-5-yl)-4-phenyl-2,3-dihydrobenzo[1, 5]thiazepine **94a** showed signals at δ: 3.06 (t, 1H, J = 12.7 Hz) for H_X, 3.30 (dd, 1H, J = 13.0 H_z, J = 4.6 Hz) for H_a, 4.98 (dd, 1H, J = 12.6 Hz, J = 4.6 Hz) for H_b, and 6.0 (2H, s) for dioxymethylene group, and peaks for aromatic protons appeared in the range of δ: 7.23–7.8 ppm [25].

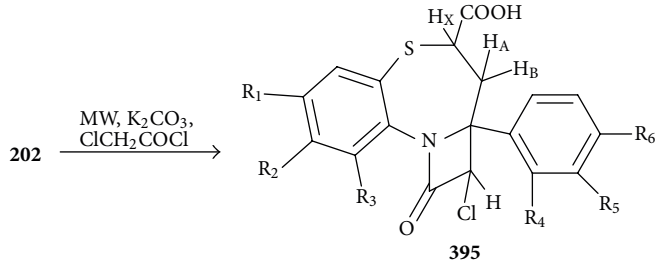
The structures of all azeto [2, 1-*d*][1, 5]benzothiazepines **99a–f**, as well as the product **101,** have been elucidated



Scheme 70: Reduction of dihydro-1,5-benzothiazepine with either $NaBH_4$ or with *o*-ATP or DAPDS, as well as with H_2 using Pt.



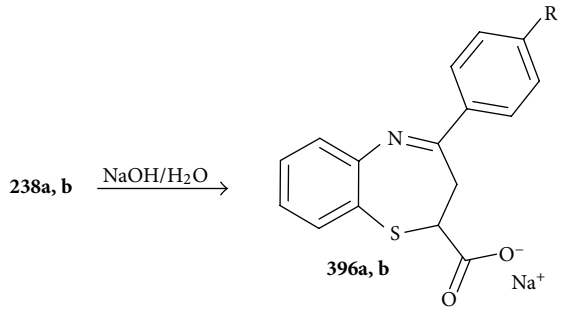
Scheme 71: Extrusion of sulfur atom of 1,5-benzothiazepine.



Azeto-[2,1-*d*][1,5]benzothiazepines (**395a–m**)

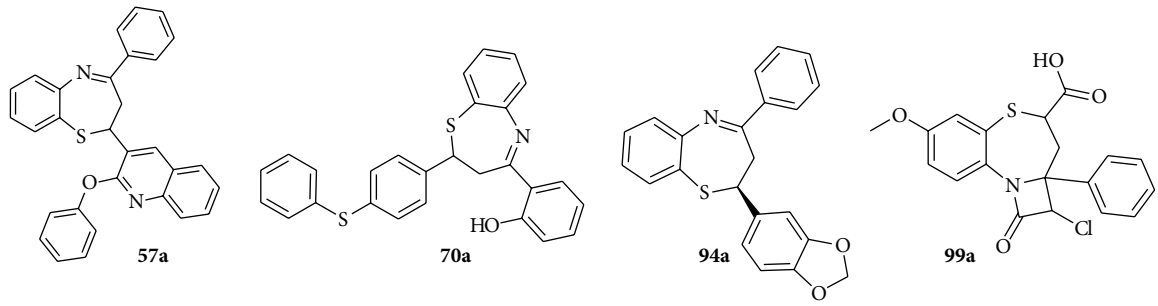
395	R_1	R_2	R_3	R_4	R_5	R_6	Time (min)	Yield (%)
(a)	CH_3	H	H	H	H	F	4	78
(b)	F	H	H	H	H	F	5	80
(c)	Cl	H	H	H	H	F	5	82
(d)	Br	H	H	H	H	F	3	85
(e)	OCH_3	H	H	H	H	F	5	83
(f)	OC_2H_5	H	H	CH_3	H	F	4	85
(g)	C_2H_5	H	H	CH_3	H	F	4	76
(h)	H	CF_3	H	H	Cl	H	6	75
(i)	H	H	Br	H	CF_3	H	5	80
(j)	CF_3	H	H	H	H	OH	4	84
(k)	H	H	Cl	H	H	F	3	75
(l)	H	H	CF_3	CH_3	H	F	6	85
(m)	H	CH_3	CH_3	H	CF_3	H	5	82

Scheme 72: Reactions of 2-carboxy-2,3-dihydro-1,5-benzothiazepines with K_2CO_3 and chloroacetyl chloride under microwave irradiation.

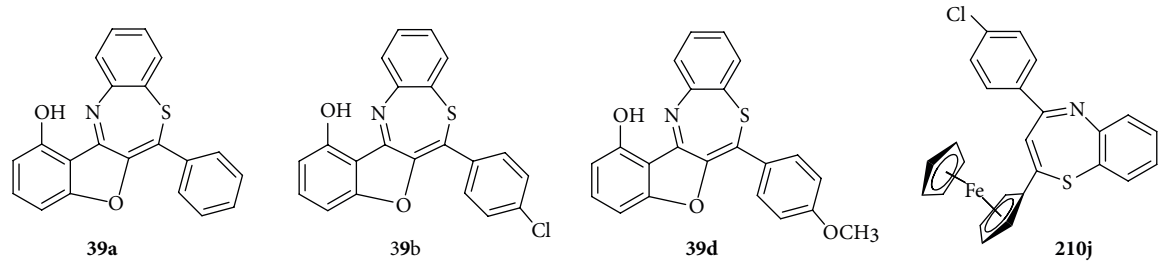


Scheme 73: Hydrolysis of sodium salts of 1,5-benzothiazepine-2-carboxylic acid.

by spectroscopic studies. Theoretically, compound **99a–f** exhibiting two chiral centers could exist in two diastereomeric forms; however, the ^{1}H NMR spectra and chromatographic studies of the isolated compounds indicated the formation of only one diastereomer. For example, the PMR spectrum ($CDCl_3$, 300.15 MHz) of 2-chloro-7-methoxy-1-oxo-2a-phenyl-2,2a,3,4-tetrahydro-1*H*-azeto[1, 2-*d*]benzo[1, 5]thiaz-epine-4-carboxylic acid



Scheme 74



Scheme 75

99a displayed signals at δ: 3.75 (s, 3H,OC**H**$_3$), 3.08 (dd, 1H, **H**$_A$, J_{A-B} = 15.28, J_{A-X} = 9.15 H$_z$), 3.62 (dd, 1H, **H**$_B$, J_{A-B} = 15.28, J_{B-X} = 8.12 Hz), 4.02 (dd, 1H, **H**$_X$, J_{A-X} = 9.15 H$_z$, J_{B-X} = 8.12 H$_z$), 5.12 (s, 1H, Cl–C**H**), 6.58–7.79 (m, 8H, Ar–**H**), AND 8.47 (bs, 1H, COO**H**) ppm. The spectrum ($CDCl_3$, 300.15 MHZ) of 2-chloro-3-(chloromethyl)-9-methoxy-1-oxo-4a-phenyl-1,4a,5,6-tetrahydrobenzo[1, 3]oxazino[3, 2-*d*][1, 5]thiazepine-6-carboxylic acid **101** showed signals at δ: 2.67 (dd, 1H, **H**A, J_{A-B} = 14.98 H$_z$, J_{A-X} = 8.89 H$_z$), 3.25 (dd, 1H, **H**$_B$, J_{A-B} = 14.98 H$_z$, J_{B-X} = 8.12 H$_z$), 3.58 (s, 2H, C**H**$_2$Cl), 3.86 (s, 3H, OCH_3), 4.06 (dd, **H**$_X$, J_{A-X} = 8.89 H$_z$, J_{B-X} = 8.12 Hz), and 6.98–7.32 (m, 8H, Ar–**H**) ppm [26].

The ^{1}H NMR spectra of **107a–d**, generally, showed the enamine methyl (–N–C=C–Me) group at 2.60–2.65 ppm, the NH group at 6.19–6.23 ppm and S–CH group at the C-2 position as a singlet at 5.89–6.14 ppm. However, in the ^{1}H NMR spectra of **108e**, the imine methyl (–N=C–Me) group went up field at 2.29 ppm, the NH signal disappeared, the S–CH group at the C-2 position appeared as doublets at 5.20–5.23 (J = 9.2 Hz), and the CH group at the C-3 position in the seven-membered ring of benzothiazepine appeared as doublets at 3.70–3.72 ppm (J = 9.2 Hz), owing to their vicinal coupling [29].

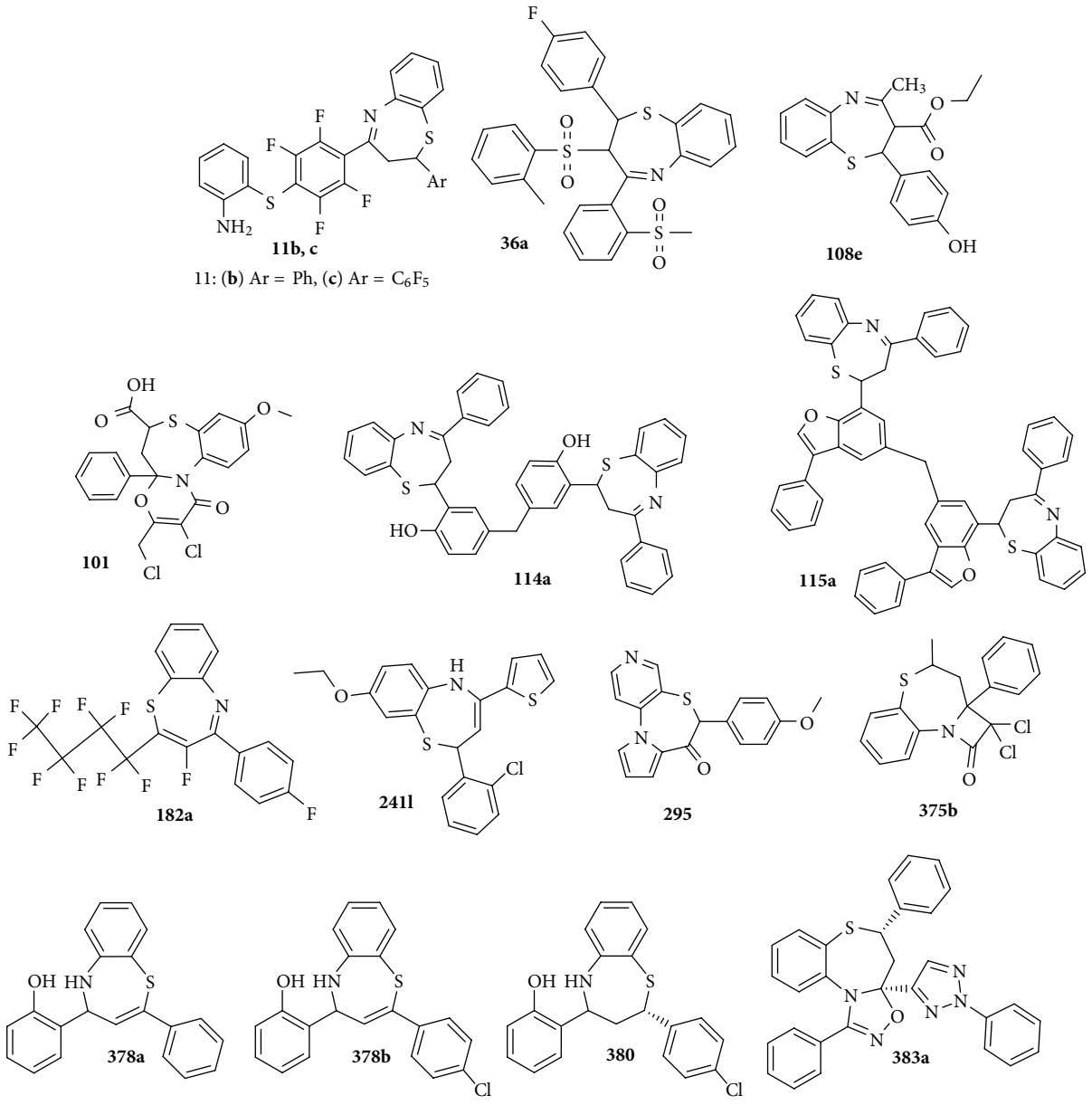
The proton spectra (DMSO-d_6) of (*E*)-4,4′-methylenebis(2-((*E*)-4-phenyl-2,3-dihydrobenzo[1, 5]thiazepin-2-yl)phenol) **114a** and bis(3-phenyl-7-((*E*)-4-phenyl-2,3-dihydrobenzo[1, 5]thiazepin-2-yl)benzofuran-5-yl)methane **115a** revealed signals at δ = 3.21 (2H, dd, J_{AB} = 12.7, J_{AX} = 11.4 H$_z$, H$_A$), 3.39 (2H, dd, J_{BX} = 5.1, J_{BA} = 12.7 H$_z$, H$_B$), 3.72 (2H, s, CH_2), 4.82 (2H, dd, J_{XA} = 11.4, J_{XB} = 5.1 Hz, H$_X$), 5.72 (2H, s, OH), 6.42 (2H, d, J = 9.1 H$_z$, ArH), 7.18–7.47 (14H, m, ArH), and 7.62–7.75 (8H, m, ArH) and at 3.31 (2H, dd, J_{AB} = 12.7, J_{AX} = 11.4 H$_z$, H$_A$,) 3.62 (2H, dd, J_{BX} = 5.1, J_{BA} = 12.7 Hz, H$_B$), 3.91 (2H, s, CH_2), 5.47 (2H, dd, J_{XA} = 11.4, J_{XB} = 5.1 Hz, H$_X$), 6.84 (2H, s, ArH), 7.19–7.35 (8H, m, ArH), 7.40–7.47 (8H, m, ArH), 7.55–7.65 (10H, m, ArH), 7.78 (2H, s, ArH), and 7.91 (4H, d, J = 8.1 Hz, ArH), respectively [30].

^{1}H NMR (500 MHz) of **182a** showed signals at δ = 7.15–7.30 (m, 4 H, H$_{arom}$), 7.40–7.55 (m, 2 H, H$_{arom}$), and 7.90–8.05 (m, 2 H, H$_{arom}$) ppm [44–47].

The PMR (300 MHz) of (*Z*)-2-(2-chlorophenyl)-8-ethoxy-4-(thiophen-2-yl)-2,5-dihydrobenzo[1, 5]thiazepine **241l** revealed the following signals: C–2-H (d, 1H, J = 6.92); C–3-H (d, 1H, J = 8.02); C–8-XH: 1.44 (3H, t, J = 7); 4.10 (2H, q, J = 7); aromatic protons (m, 7.00–7.99) ppm [60].

^{1}H-NMR ($CDCl_3$, 200 MHz) of 6-(4-methoxyphenyl)pyrido[3, 4-*b*]pyrrolo[1, 2-*d*][1, 5]thiazepin-7(6H)-one **295** showed signals at δ = 3.76 (3H, s, OCH_3), 4.30 (1H, s, CH), 6.41 (1H, t, pyrrole-H), 6.76 (2H, d, J = 8.4 Hz, pyrrole-H), 7.12~7.21 (5H, m, ArH), 8.50 (1H, d, J = 7.2 Hz, ArH), and 8.68 (1H, s, ArH) [72].

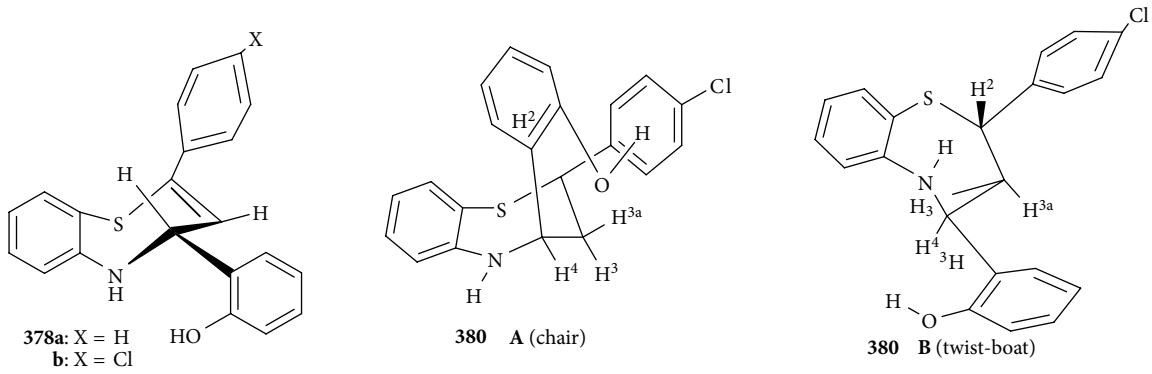
The relative stereo configurations of 2a,4-disubstituted 2-phthalimido-, 2,2-dichloro-, or 2-phenoxy-2,2a,3,4-tetrahydro-1*H*-azeto[2, 1-*d*][1, 5]benzothiazepin-1-ones **373a**, **375b**, and **376a** were identified based on the same reaction mechanism and NOESY spectra in which C_2–H shows a long-distance coupling with C_3–Ha for products **373a**, **374i**, and **376a**. The observation indicated that these two hydrogen atoms should be *cis*. On the basis of coupling constants (J) and the Karplus equation, C_3–He and C_4–H have an angle near 90° (J < 2 Hz) and C_3–Ha and C_4–H an angle near 180° (J around 10 Hz). This indicates that C_2–H and C_4–H are *trans* for products **373a**, **373b**, and **376a**. Thus, R^1 is *trans* to phthalimido, chloro, or phenoxy group in the products **373a**, **374i**, and **376a**. R^1 is also *trans* to R^2 for all products,



Scheme 76

which is known from starting materials. Consequently, R^2 and phthalimido, chloro, or phenoxy group in the products **373a**, **374i**, and **376a** are *cis*. Namely, the cycloaddition is a stereospecific reaction. The ^{1}H-NMR spectra of cycloadducts **373–376** indicate that only one pair of diastereomers were present in each of the cycloaddition reactions [80].

6.4. ^{13}*C NMR.* ^{13}C NMR ($CDCl_3$, 400 MHz) δ, 100.6 MHz of *trans*-2-(4″-chlorophenyl)-4-(2′-hydroxyphenyl)-2,3,4,5-tetrahydro-1,5-benzothiazepine **380** revealed signals at 118.1 (C-3′), 120.3 (C-5′), 122.5 (C-6), 125.3 (C-8), 125.5 (C-10), 126.4 (C-9a), 128.7 (C-2″/6″), 128.8 (C-6′), 129.2 (C-3″/5″), 129.7 and 129.8 (C-7 and C-40), 133.2 (C-4″), 134.2 (C-9), 144.0 (C-1″), 146.4 (C-5a), and 159.6 (C-2′) ppm [9]. The spectrum ($CDCl_3$, 400 MHz) δ, 100.6 MHz of 2-phenyl-4-(2′-hydroxyphenyl)-4,5-dihydro-1,5-benzothiazepine **378a** showed signals at 61.2 (C-4), 117.6 (C-6), 118.6 (C-3′), 120.3 (C-8), 120.4 (C-1′), 122.6 (C-4′), 123.1 (C-9a), 123.8 (C-3), 126.0 (C-5′), 126.3 (C-6′), 127.5 (C-4″), 128.4 (C-3″/5″), 129.1 (C-2″/6″), 130.4 (C-9), 130.6 (C-7), 131.4 (C-2), 135.6 (C-1″), 141.1 (C-5a), and 155.8 (C-2′) ppm [9]. In the ^{13}C NMR spectrum of **378a** (Scheme 76), there is only one peak in the aliphatic region at δ = 61.2 ppm (CH) [9]. Also, the spectrum of 2-(4″-chlorophenyl)-4-(2′-hydroxyphenyl)-4,5-dihydro-1,5-benzothiazepine **378b** ($CDCl_3$, δ, 400 MHz) displayed the following: 61.5 (C-4), 117.6 (C-6), 118.3 (C-3′), 120.2 (C-8), 120.2 (C-1′), 122.6 (C-4′), 123.4 (C-3 and C-9a), 126.1 (C-5′), 126.3 (C-6′), 134.4 (C-4″), 129.1 (C-3″/5″), 130.2 (C-9), 130.4



378a: X = H
b: X = Cl

380 **A** (chair)

380 **B** (twist-boat)

Scheme 77

(C-2″/6″), 130.5 (C-7), 132.9 (C-2), 134.4 (C-1″), 141.6 (C-5a), and 155.9 (C-2′) ppm [9]. The ^{13}C NMR ($CDCl_3$, 250 MHz) of **182a** showed the following signals at δ = 116.0 (s, C_{arom}), 125.0 (s, C-2′), 126.0 (s, C-5′), 127.8 (s, C-3′), 130.6 (s, C_{arom}), 131.1 (s, C-6′), 132.7 (s, C-4′), 148.8 (s, C-1′), 153.0 (d, $^1J_{C,F}$ = 301.0 Hz, C-3), 153.6 (m, C-2), 155.4 (C_{arom}), 157.0 (d, $^2J_{C,F}$ = 27.0 Hz, C-4), and 165.1 (d, $^1J_{C,F}$ = 253.9 Hz, CF_{arom}) ppm [44–47].

6.5. ^{19}F NMR. ^{19}F NMR ($CDCl_3$, 500 MHz) of (*E*)-2-(2,3,5,6-tetrafluoro-4-(2-phenyl-2,3-dihydrobenzo [1, 5]thiazepin-4-yl)phenylthio)aniline**11b:** 0.53, 6.81, and 22.27 (intensity values: 2 : 1 : 2) and of **11c**: 21.37, 28.74 (1 : 1) [5]. The spectrum of 3-Fluoro-4-(4′-fluorophenyl)-2-(perfluorobutyl) benzo-1,5-thiazepine **182a** ($CDCl_3$, 500 MHZ) displayed signals at: δ = −81.4 (m, CF_3), −82.8 (m, CF), −107.4 (m, CF_{arom}), −108.1 (m, $CF_2{}^a$), −123.0 (m, $CF_2{}^b$), and −126.5 (m, CF_2) ppm [44–47]. See Scheme 77.

*6.5.1. Stereo Chemistry of Benzothiazepines **387a, 387b,** and **380**.* The ^{1}H NMR spectrum of **378a** shows two sharp signals at δ = 5.95 and 4.97 ppm besides the signals in the aromatic and olefinic region. The proton at δ = 4.97 ppm is attached to the carbon at δ = 61.2 ppm as shown by the HMQC spectrum. This proves the presence of a –(H-4)–(C-4)–N– fragment. The hydrogen at δ = 5.95 ppm is attached to the carbon at δ = 126.0 ppm which is a typical sp^2-CH region. The assignment of this CH fragment to H-3/C-3 is proven by the HMBC spectrum correlating C-3 and H-4. H-4 showed a correlation (three-bond coupling) to the aromatic carbon carrying the OH group (C-2′). The surprisingly small vicinal coupling constant ^3J (H-3, H-4) = 1.3 Hz indicates that the respective torsion angle (H-3/C-3/C-4/H-4) is close to 90°. This allows to define the preferred conformation of **378a** and **378b** as a half-chair with a quasiequatorial phenol substituent at C-4 [9].

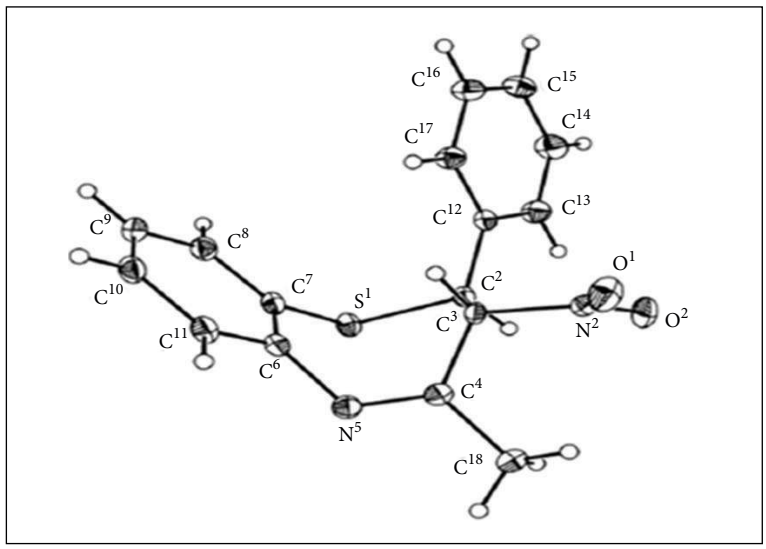
There are only two conceivable conformations of the *trans*-configurated **380**—the *cis*-configuration can be excluded—which fit to this combination of couplings, structures **A** (chair) and **B** (twist-boat). Semiempirical calculations (AM1) of **380** slightly favour the twist-boat conformation **B**, but the difference of ca 1 kJ/mol is possibly within the error limits of the calculation. If, however, the geometry of the calculated structures and the experimental vicinal ^{1}H,^{1}H coupling constants are evaluated using the Karplus equation, the chair conformation is more plausible. Especially, the coupling constant of 4.0 Hz for the H^4–C^4–C^3–H^{3a} fragment fits much better to the chair (torsion angle = −58°) than to the half-boat conformation (torsion angle = −81°) [9].

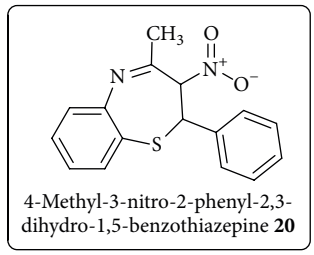
7. X-Ray Diffraction Pattern of Some Selected 1,5-Benzo- and Pair Benzothiazepine Derivatives

7.1. X-Ray Diffraction Pattern of 4-Methyl-3-nitro-2-phenyl-2,3-dihydro-1,5-benzothiazepine. The X-ray diffraction study showed that in the molecule of compound **20**, the seven-membered heterocycle has a distorted *boat* conformation, with the deviation from the plane of the atoms C^3, C^6, and C^7 by 0.599(5), 1.214(7), and 1.226(7) Å, respectively. This conformation, in turn, leads to a lack of conjugation of the C^4–N^5 double bond with the aromatic ring, which is confirmed by the values of bond lengths [C^4–N^5 1.2742(16) Å, N^5–C^6 1.4136(15) Å] and torsion angle $C^4N^5C^6C^7$ 52.64(16)° (Scheme 78).

The location of the substituents at the C^2–C^3 corresponds to staggered conformation the hydrogen atoms are almost antiperiplanar to each other (torsion angle $H^{2A}C^2C^3H^{3A}$ is 167°). In the crystal, the molecules are packed along *b* axis due to sufficiently strong CH···O interaction between C^2–H^{2A} group and the oxygen atom of the nitro group (2.36 Å), as well as due to a shortcontact between the electron pair of the sulfur atom and the π-density of benzothiazepine ring (the shortest S···C contact is 3.48 Å) [6].

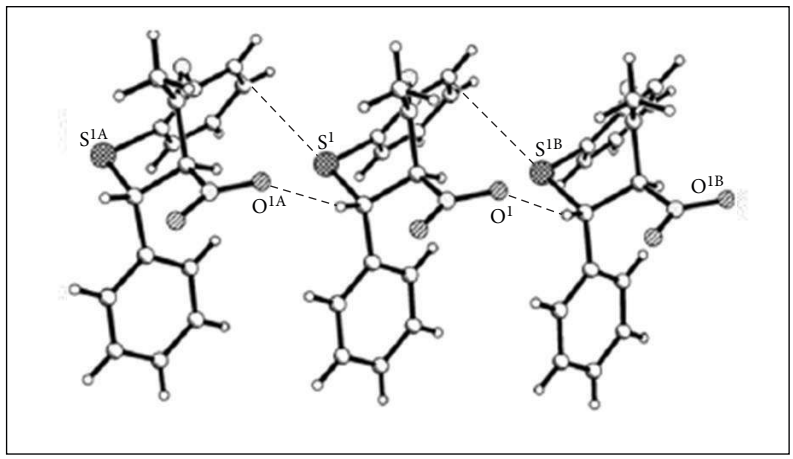
7.1.1. Crystal Structures of a Pair of N-Chloroacetyl-2,3,4,5-tetrahydro-2,2,4-trimethyl-1,5-benzothiazepine and N-Chloroacetyl-2,3,4,5-tetrahydro-2,2,4-trimethyl-1,5-benzothiazepine. The benzo derivatives of azepines, like benzothiazepines, constitute a class of compounds with specific applications.





4-Methyl-3-nitro-2-phenyl-2,3-dihydro-1,5-benzothiazepine **20**

Scheme 78: General view of 4-methyl-3-nitro-2-phenyll-2,3-dihydro-1,5-benzothiazepine molecule **20** in the representation of atomic thermal vibration ellipsoids (P = 50%).

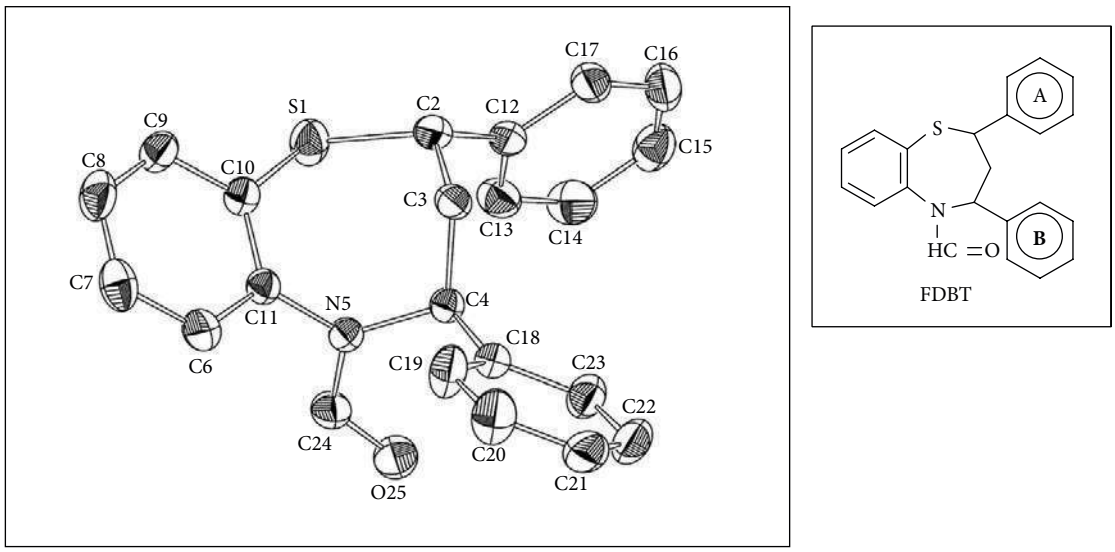


Scheme 79: Fragment of crystal packing of compound **20**, illustrating the C–H···O bonding and S···π interaction.

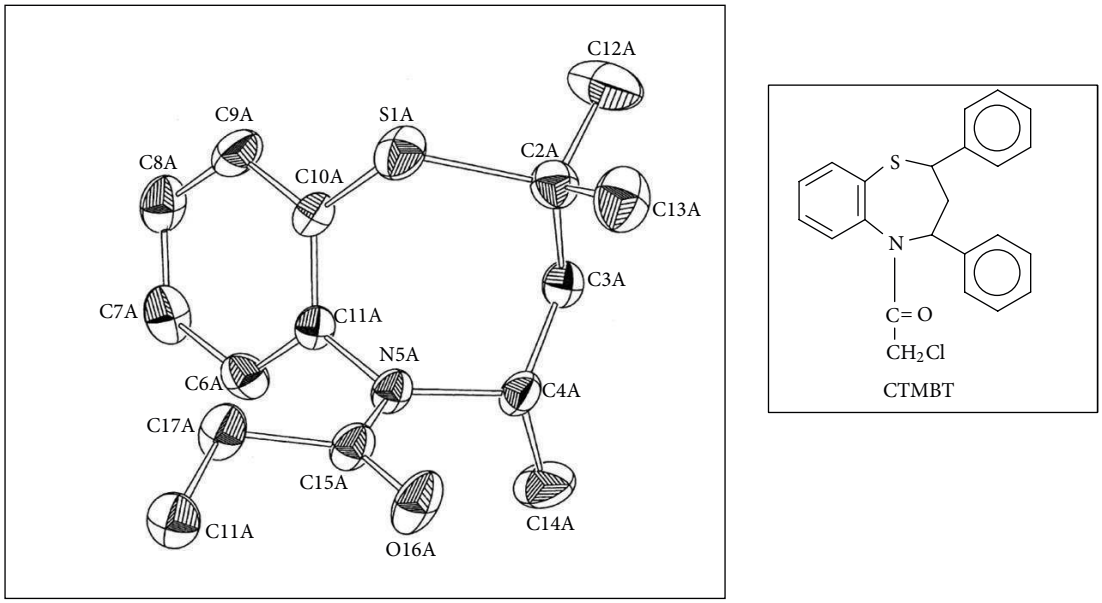
Colorless crystals of *N*-formyl-2,3,4,5-tetrahydro-2,4-diphenyl-1,5-benzothiazepine (FDPBT) and of *N*-chloroacetyl-2,3,4,5-tetrahydro-2,2,4-trimethyl-1,5-benzothiazepine CTMBT were chosen for the single crystal X-ray data collection. The Enraf-NoniusCAD4 diffractometer with graphite monochromated CuKα radiation employing $\omega - 2\theta$ scan mode was used for data collection. The perspective views of the molecules using ORTEPIII are shown for FDPBT and for CTMBT. The interatomic distances spanned by bonds in the two benzothiazepines are in good agreement with each other. The two structural entities in CTMBT duplicate each other in relation to atomic intimacies, as seen from the bond distances and bond angles. In general, N-formyl-2,3,4,5-tetrahydro-2,4-diphenyl-1,5-benzothiazepine (FDPBT), $C_{22}H_{19}$ N O S, F.W = 345.44, monoclinic, $P2_1$ = c, α = 11.2268(1)À, β = 9.0297(1)À, c = 18.3813(1)À, β = 104.77(1)°, V = 1801.8(3)À^3, Z = 4, D_{calc} = 1.273 Mg/m^3, μ = 1.651 mm^{-1}, F000 = 728, CuKα = 1.5418 À, final *R1* and *wR2* are 0.0757 and 0.1752, respectively. *N*-Chloroacetyl-2,3,4,5-tetrahydro-2,2,4-trimethyl-1,5-benzothiazepine(CT-MBT), $C_{14}H_{17}$Cl N O S, F.W = 282.80, monoclinic, $P2_1$ = c, α = 12.9740(1)À, b = 13.3530(1)À, c = 17.0790(1)À, β = 91.12(1)°, V = 2958.2(4)À^3, Z = 8, D_{calc} = 1.270 Mg/m^3, μ = 3.504 mm^{-1}, F000 = 1192, CuKα = 1.5418 À, final *R1* and *wR2* are 0.0610 and 0.1609, respectively. The septilateral ring of the benzothiazepine in the two structures adheres to an identical *boat* conformation. The prow and stern angles are nearly the same for both the medium-sized rings [81] (Schemes 79, 80, and 81).

8. Applications (Selected Patents)

Several patents have been reported for 2-azetidinone derivatives (included in combination with several tetrahydro-1,5-benzothiazepine derivatives or pharmaceutically acceptable salts, solvates, solvates of such salts, and prodrugs thereof



Scheme 80: *ORTEP diagram* of *N*-Formyl-2,3,4,5-tetrahydro-2,4-diphenyl-1,5-benzothiazepine (FDPBT).



Scheme 81: *ORTEP diagram* of *N*- Chloroacetyl-2,3,4,5-tetrahydro-2,2,4-trimethyl-1,5-benzo-thiazepine (CTMBT).

for the treatment of hyperlipidaemic conditions). These 2-azetidinones possess chloesterol absorption inhibitory activity and accordingly of value in the treatment of disease states associated with hyperlipidaemic conditions, possess ileal bile acid transport (IBAT) inhibitory activity as well of value in the treatment of disease states associated with hyperlipidaemic conditions. They are therefore useful in methods of treatment of a warm-blooded animal, such as man [82–86]. Some other 1,5-benziazepine derivatives and their related intermediates were patented for their use in medicine, particularly in the prophylaxis and treatment of hyperlipidemic conditions and associated conditions such as atherosclerosis [87]. The process for preparing diltiazem and novel intermediates for use in that process, has been patented. Diltiazem is: (2*S*-*cis*)-3-(acyloxy)-5-[2-(dimethylamino) ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiaz-epine-4(5*H*)-one. Diltiazem is a calcium channel blocker with coronary vasodilating, antihypertensive, and psychotropic activity. Vasodilating action is the highest selling chiral cardiac prescription drug, which was synthesized by resolution methods [88]. Substituted piperazines of azepines, oxazepines, and 1,5-thiazepines have been reported as antipsychotic and are of use as antagonists of dopamine D_2 receptor and as agents for the treatment of psychosis and bipolar disorders [89].

Some thiazolo-1,5-thiazepines and analogs and derivatives were patented as anti-integrase inhibitors. These compounds are useful as treatments for HIV disease [90]. Recently, some molecularly diverse coumarins clubbed with benzothiazepines, and its aza-analogs-benzodiazepines by molecular hybridization were screened for their *M. tuberculosis* activity against H(37)Rv strains using microplate alamar blue assay (MABA). Three compounds, in-between, were found significantly active in primary anti-tuberculosis (TB) assay at MIC $< 6.25\,\mu$M. IC (50) values of two of these benzothiazepine products in level-2 screening were observed as $>10\,\mu$g/mL and $3.63\,\mu$g/mL, respectively [81].

9. Conclusion and Future Look

The presented paper comprises the recent ten-year survey for most published articles about benzo[1, 5]thiazepines and their related derivatives: synthesis, chemical, physical, and biological properties. The common strategy for the construction of the 1,5-benzothiazepine moiety is the reaction of 1,3-diarylprop-2-enones with *o*-aminothiophenol and 1,3-difunctional three-carbon building blocks. Among them, α,β-unsaturated carbonyl compounds such as enones and ynones are suited best for Michael addition and subsequent cyclocondensation. The various reported methodologies involve the use of inorganic supports such as alumina, silica gel, and clay under microwave irradiation, AcOH or TFA, HCl, piperidine, and also the catalysts such as $BF_3{\cdot}Et_2O$, $NaBH_4$, polyphosphoric acid (PPA)/SiO_2, MgO/$POCl_3$, amberlyst-15, $Yb(OTf)_3$, Al_2O_3/P_2O_5, AcOH/MW, sulfated zirconia, *N*-bromosuccinimide (NBS), $Ga(OTf)_3$, and sodium dodecyl sulfate (SDS) with the utility of ultrasound irradiation in organic transformation have been used to improve reaction efficiency. The 1,5-benzothiazepine framework has been identified as a pluripotent pharmacophore with derivatives encompassing CNS-acting agents, anti-HIV, anti-Tuberculosis (TB) and anticancer drugs, angiotensin converting enzyme inhibitors, antimicrobial and antifungal compounds, calmodulin antagonists, bradykinin receptor agonists, and Ca^{2+} blockers. In addition, dihydro 1,5-benzothiazepines have become increasingly interesting since many derivatives exhibit antifungal, antibacterial, antifeedant, anti-inflammatory, analgesic, and anticonvulsant activity. Likewise, the related 1,5-benzothiazepines display a comparable spectrum of biological activity. Moreover, benzothiazepines possess highly interesting pharmaceutical properties and a diversity-oriented synthesis approach using the advantages of multicomponent reactions.

It is hoped in the future to find a milder, selective, nonhazardous, and inexpensive solvents and there is necessity to develop a more effective synthetic procedure for the synthesis of 1,5-benzothiazepines. Also, it is hoped to discover other new active benzo[1, 5]thiazepines and other related derivatives for solving the most nowadays serious human diabetic as well as Alzheimer's disease problems that cause health troubles for millions of human beings around the world.

Abbreviations

TPP:	Tetraphenylporphyrin
NMM:	N-Methylmorpholine
DIAD:	Diisopropyl azodicarboxylate
HATU:	Peptide coupling reagent: 2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium
DBU:	1,8-Diazabicyclo[5.4.0]undec-7-ene
EDC:	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride
Edc:	Ethylene dichloride
PTC:	*p*-Toluenesulphonyl chloride
DCM:	Dichloromethane
TBAB:	Tetrabutylammonium bromide
TFA:	Trifluoroacetic acid
TEBA-Cl:	Triethylbenzylammonium chloride
CAN:	Ceric ammonium nitrate
La Y Zeolite:	Lanthanum-containing Y zeolite
DAPDS:	Di o-aminophenyl disulphide
o-ATP:	Adenosine-5′-triphosphate
TITD:	Tetraisopropylthiuram disulfide
m-CPBA:	*meta*-Chloroperbenzoic acid
HMDS:	Hexamethyldisilazane
DCC:	1,3-Dicyclohexylcarbodiimide or N,N-dicyclohexylcarbodiimide
SmI_2:	Samarium diiodide (Kagan Reagent)
DMD:	Dimethyldioxirane
RCM:	Ring-closing metathesis
MCR:	Multicomponent reaction
Oxone:	Potassium peroxymonosulfate
IBAT:	Ileal bile acid transport.

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